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STRUCTURAL, SYNTHETIC, AND ^{13}CMR STUDIES ON FUNGAL METABOLITES AND RELATED COMPOUNDS

by

© STEVEN FUNG

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
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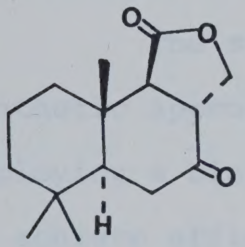
ABSTRACT

Part I of the thesis describes an examination of the metabolites of the bird's nest fungus *Mycocalia reticulata* Petch. The bicyclofarnesane sesquiterpenes 7-ketodihydrodrimenin (1), 7β-hydroxydihydrodrimenin (2), and 6α,7β-dihydroxydihydrodrimenin (3) have been isolated and characterized. These compounds have not been obtained



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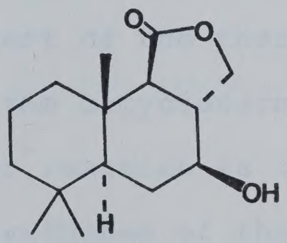

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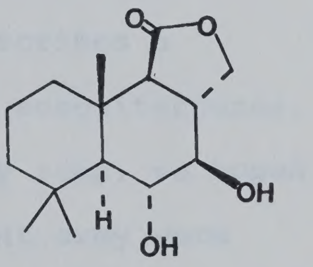

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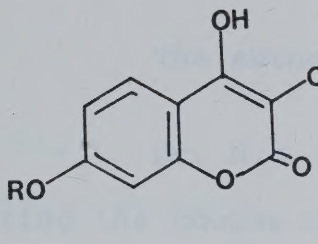
previously from natural sources, although 1 and 2 are known transformation products of other natural products. Compound 3 is new, and its structure was established by physical methods. The known triterpenoid glochidone, β-sitosterol, and ergosterol were also isolated as well as several previously undescribed acidic metabolites. One of these has tentatively been assigned the coumarin structure 4. A sesquiterpenoid acid has been isolated as its methyl ester and has been identified as the diosphenol 5. Preliminary characterization of several new triterpenoid acids is reported.



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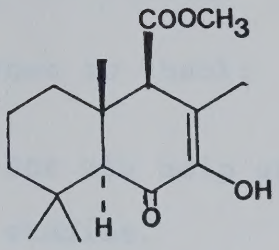

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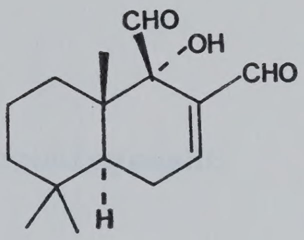

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The second part of the thesis describes a synthetic approach to the bicyclofarnesane sesquiterpenes. Employing a Diels-Alder reaction as the key step, we hoped to achieve efficient syntheses of the potent army worm antifeedant warburganal (6) as well as the bicyclofarnesane lactones 1, 2, and 3 isolated from *M. reticulata*.

The third part of the thesis describes the syntheses and a ^{13}Cmr study of (±)-geosmin and related 10-methyldecalols. An examination of an interesting γ-substituent effect in the ^{13}Cmr spectra of these compounds is presented. In decalol systems it was found that hydroxyl substituents deshield antiperiplanar carbons by as much as 6 ppm when bonded through fully substituted carbons. Methyl substituents were also found to deshield antiperiplanar carbons but to a lesser extent.

ACKNOWLEDGEMENTS

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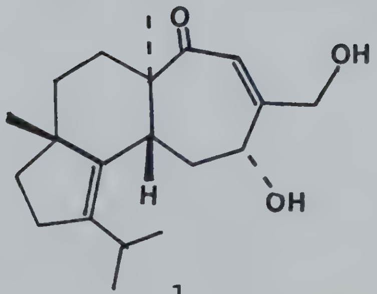
I: METABOLITES OF THE BIRD'S NEST FUNGUS *MYCOCALIA RETICULATA*[1]

INTRODUCTION

> Anyone may become impatient if asked, too often, to explain that bird's nest fungi have never been found in bird's nests and have nothing at all to do with bird's nest soup.
>
> The first encounter with a member of the gasteromycete fungi known as the Nidulariaceae or bird's nest fungi usually engenders in the mind of the observer, a feeling of delight and wonder: delight certainly, because of the symmetry and artistic form of the small vase-shaped or bell-shaped fruit bodies; wonder probably if the observer is at all curious as to why the little cups should be filled with small lentil-shaped bodies resembling seeds. The whole fruit body bears a general resemblance to a miniature bird's nest containing eggs, whence the common English name bird's nest fungi. The Latin name for the family to which these fungi belong is Nidulariaceae, which is derived from *nidula*, meaning a little nest.[2]

Liquid cultures of the small bird's nest fungi produce a variety of interesting compounds. For example, *Cyathus helenae* Brodie[3] produces the novel diterpenoid cyathin A_3 (1). A degraded eudesmane sesquiterpenoid cybullol (2) has been isolated from *C. bulleri* Brodie,[4] and a new xanthone 3 from *C. intermedius*.[5]



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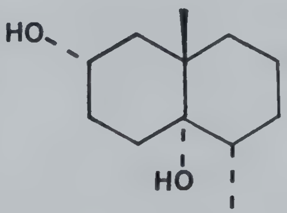

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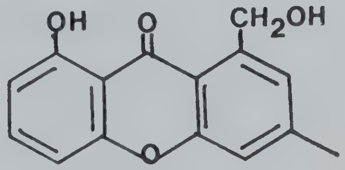

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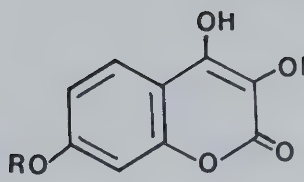
Mycocalia reticulata Petch,[6] a tropical and subtropical species of the bird's nest fungi family, was first discovered in Ceylon in 1919 by Petch. It has also been found in France and the southern United States.

Part I of the thesis describes an examination of cultures of M. reticulata in a search for interesting metabolites.

M. reticulata was grown in 'still surface' culture on a liquid medium and the culture broth was extracted with ethyl acetate. The crude extract was originally partitioned between several solvents, including base and acid separation. Only one compound, assigned coumarin structure 4 was isolated from these fractions. The mixtures of components appeared to be very complex. Subsequently, the crude extract was separated only into acidic and neutral fractions. The neutral fraction yielded drimanes 5, 6a, and 7a, the triterpenoid glochidone (8), and β-sitosterol (9). The acidic fraction gave various triterpenoid acids and a sesquiterpenoid acid isolated as its methyl ester and suggested to have structure 10. It was also noted that the mycelia of M. reticulata contained ergosterol (11).



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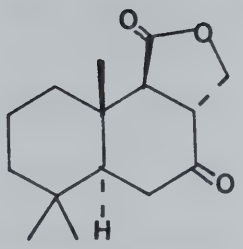

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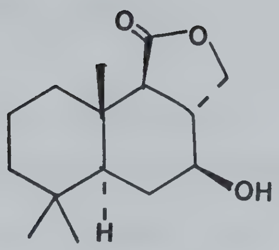

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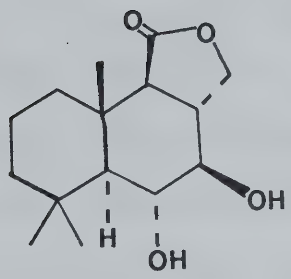

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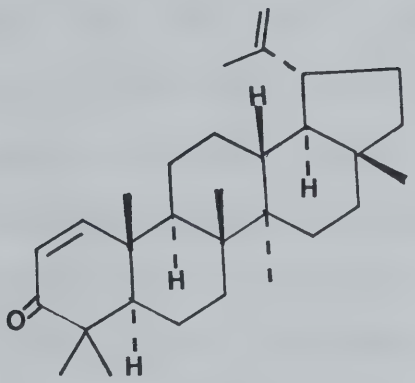

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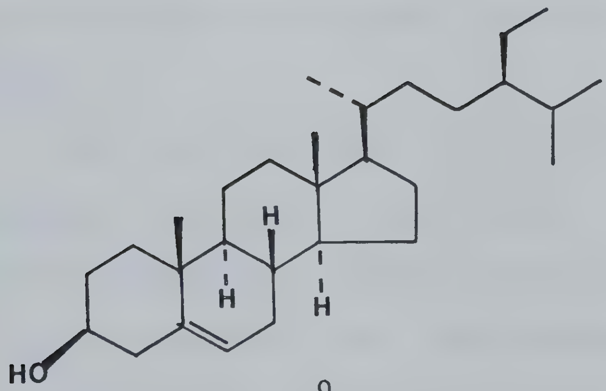

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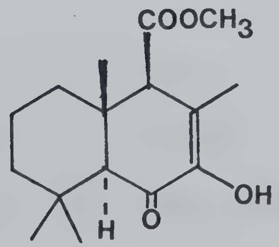
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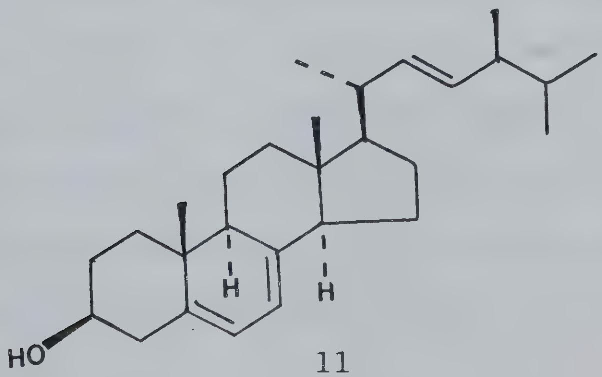

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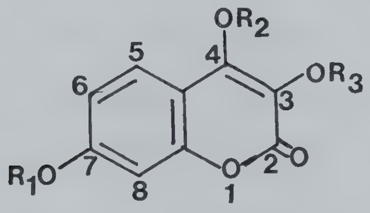
DISCUSSION AND RESULTS

The crude ethyl acetate extract of M. reticulata contained a complex mixture of many compounds as evidenced by thin layer chromatography (tlc). In an attempt to facilitate the isolation of individual components, the crude extract was first partitioned between various solvents. The crude extract was dissolved in 80% aqueous methanol and partitioned with Skellysolve B and then toluene. The remaining aqueous methanol layer was concentrated and then separated into acidic, basic, and neutral fractions. We thus had five fractions: Skellysolve B, toluene, acidic, basic, and neutral. The bulk of the material was contained in the toluene and neutral fractions whereas the basic fraction was negligible.

The Skellysolve B fraction was examined first. Preparative tlc (ptlc) gave a small amount of a highly uv active substance. The molecular formula was determined by high resolution mass spectrometry (hrms) to be $C_{15}H_{16}O_5$. The ir spectrum showed hydroxyl (3520 cm^{-1}), carbonyl (1700), and aromatic absorptions (1590, 1500). The proton magnetic resonance (^{1}Hmr) spectrum exhibited aromatic signals at δ7.62, 7.55, and 6.92 with a coupling pattern indicative of a 1,2,4-trisubstituted benzene derivative. In addition, there are signals in the ^{1}Hmr

corresponding to an O-isopentenyl moiety: a multiplet at δ5.48 (1H), a broad doublet at 4.52 (2H), and two broad singlets at 1.80 (3H) and 1.76 (3H). A methyl ether singlet also occurs at δ3.88. The uv spectrum has absorption maxima at 220, 255, 290, and 364 nm. From the above data we proposed a 3,4,7-trisubstituted coumarin 12, where the substituents may be $-CH_3$, -H, or $-CH_2-CH=C(CH_3)_2$ with no particular order intended.



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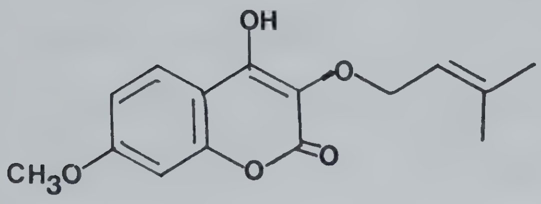
In nature, coumarins with O-substituents at C-7 are much more common than ones with O-substituents at C-6.[7] Hence the substitution in 12 is placed at C-7 rather than C-6. The hydroxyl group is placed at C-4 for two reasons. A base-induced uv shift of the 364 nm band would be expected for a C-7 hydroxyl, but no shift is observed. Hydroxyl substitution at C-3 would show intra-molecularly hydrogen-bonded hydroxyl absorption in the ir, however none is observed. Thus the methoxy and O-isopentenyl groups must be located at C-7 and C-3 (no order indended). (Note that a methoxy group at C-4 in related systems exhibits a ^{1}Hmr signal at δ4.3,[8] unlike that observed here.) Therefore,

the isolated compound is tentatively assigned structure 13 or 14. It is possible that dilute acid may hydrolyze



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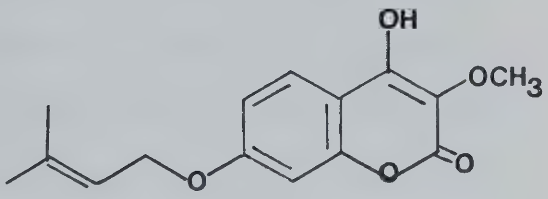

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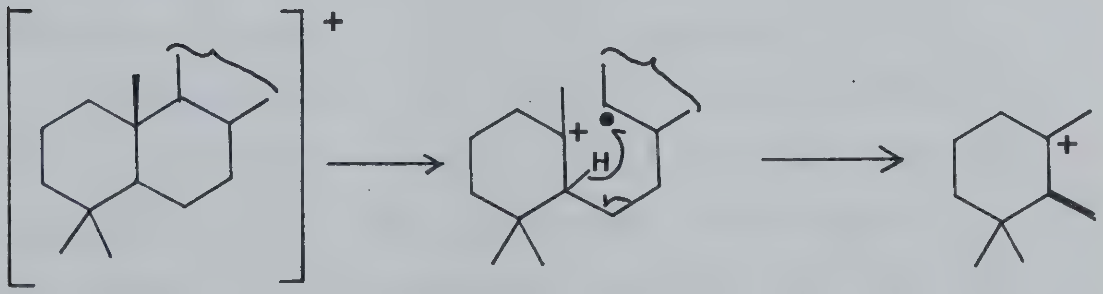
the C-3 group, thus providing a means to distinguish 13 from 14. However this experiment was not possible due to the small amount of sample available.

The other components in the Skellysolve B fraction were isolated in only very small amounts and could not be identified.

Isolation of the components from the toluene, acidic, and neutral fractions proved to be very difficult due to the complex mixture of compounds. Repeated ptlc provided no pure compounds of sufficient quantity to be analysed. The spectral data obtained from the attempted purifications indicated that many of the same compounds existed in more than one fraction. The dilution of particular compounds into more than one fraction made the isolation particularly difficult. Consequently the crude extracts were separated into only acidic and neutral fractions. Examination of the neutral fraction

will be discussed first followed by a discussion of the acidic fraction.

Preparative tlc of the neutral fraction gave three major components. Crystallization of the least polar (highest R_f value) component gave needle-like crystals, mp 120-122°. The molecular formula, $C_{15}H_{22}O_3$[*] together with the ^{1}Hmr spectrum suggested a sesquiterpenoid structure. The ^{1}Hmr spectrum exhibits three methyl singlets; two as overlapping signals at δ0.91 and one at 0.85. The ir spectrum shows carbonyl absorptions at 1770 and 1715 cm^{-1}, characteristic of a γ-lactone and a ketone respectively, thereby accounting for the three oxygens present in the molecular formula. Consideration of the above data dictates that the carbon skeleton must be at most bicyclic and contains three tertiary methyls. Furthermore, the mass spectrum shows a prominent peak at m/e 137 ($C_{10}H_{17}$). An m/e 137 fragment 17 is characteristic of higher terpenes containing the



15 16 17

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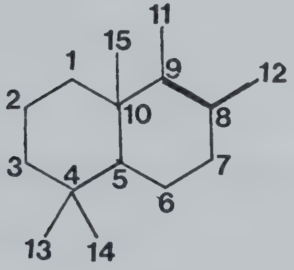
[*] The composition of all molecules and fragment ions reported in Part I of this thesis were determined by hrms.

bicyclic system 15[9] which fragments via 16. Of the known sesquiterpenes,[10] only the bicyclofarnesane (drimane) class 18 satisfy the above criteria. In addition, some are known to contain a γ-lactone moiety at C-11 or C-12.[11] After careful consideration of the spectral data, we proposed 7-ketodihydrodrimenin (5)* as the structure.



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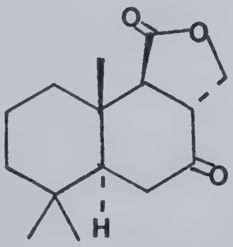

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The ^{1}Hmr spectrum (see Figure 1)† shows a two proton multiplet at δ4.45 corresponding to the AB portion of an ABX system. This signal is assigned to the protons at C-12. The X portion (δ3.28) of the ABX system exists as a broad 8-line multiplet being further coupled to a doublet at δ2.70. The signals at δ3.28 and 2.70 correspond to the C-8 and C-9 protons, respectively. The C-9 proton doublet (J = 12.5 Hz) indicates a trans-diaxial vicinal coupling to the C-8 proton, compatible with the trans-fused lactone in 5. Proton

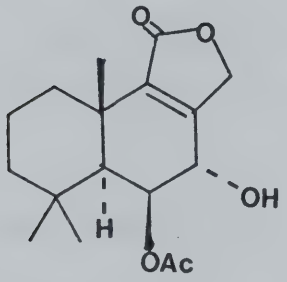
---

*Compound 5 is named according to Wenkert and Strike.[12]

†Spectra are shown as figures in the appendix.

decoupling experiments support all the above assignments.

Crystalline metabolite 5 proved to be identical* with a conversion product prepared from ugandensolide (19)



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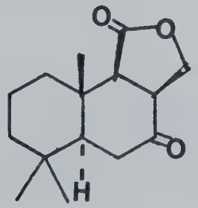
by Brooks and Draffan[11d] and also assigned structure 5.† Thus the structure and absolute configuration of 7-ketodihydrodrimenin is shown as 5.

The second ptlc component (more polar than 5) was recrystallized to give fine needles, mp 157-158°.

---

[*] The compounds are identical with respect to ir, ^{1}Hmr, ms, optical rotation, tlc, mp, and mmp. The authentic sample was kindly provided by Prof. C.J.W. Brooks.

[†] Brooks and Draffan name 7-ketodihydrodrimenin (5) as dihydro-oxoisodrimenin following the convention of Appel *et al.*[11c] who first prepared compound 5, but assigned the C-8 epimeric structure 20, the expected zinc/acetic acid reduction product from 21. Brooks and Draffan later



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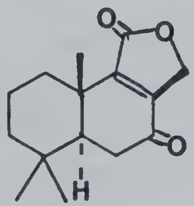

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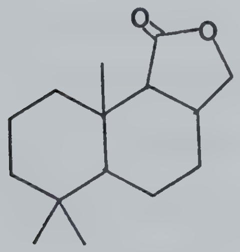
suggested structure 5 based on a ^{1}Hmr decoupling experiment indicating a large coupling constant (12.5 Hz) between the protons at C-8 and C-9. Presumably compound 20, under the reaction conditions, had undergone epimerization at C-8, relieving 1,3-diaxial interactions.

Its spectral properties (ir, ^{1}Hmr, ms) indicated a sesquiterpenoid related to 5. The mass spectrum revealed the molecular formula, $C_{15}H_{24}O_3$ and prominent fragment peaks characteristic of the ring A ($C_{10}H_{17}$) and lactone ($C_4H_5O_2$) portions in 5. The ir spectrum indicates a lactone carbonyl (1765 cm^{-1}), a hydroxyl function (3610, 3520 cm^{-1}), and the absence of ketone absorption. We therefore believed the $C_{15}H_{24}O_3$ alcohol to be a dihydrodrimenin sesquiterpene 22 with a hydroxyl function located at either C-6 or C-7. Jones' oxidation of the alcohol gave 7-ketodihydrodrimenin (5). Therefore the alcohol is formulated as 7-hydroxydihydrodrimenin (6a, C-7 stereochemistry not intended).



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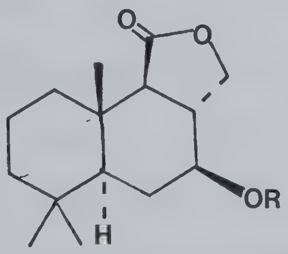


6a R = H
6b R = Ac

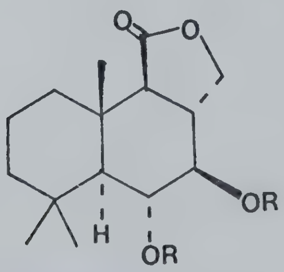
The ^{1}Hmr spectrum (see Figure 2) was assigned with the aid of proton decoupling experiments. The signal for the C-7 proton appears as a broad multiplet at δ4.11 partially overlapping the multiplet for the C-12 protons

at δ4.29. Acetylation of 7-hydroxydihydrodrimenin (6a) gave 7-acetoxydihydrodrimenin (6b) with the C-7 proton signal now appearing at δ5.12 as a broad 8-line multiplet ($W_{\frac{1}{2}}$ = 26 Hz) (see Figure 3). The nature of the C-7 proton multiplet is best explained as arising from an axial proton coupled to an equatorial proton (C-6 α-proton) and two axial protons (C-6 β-proton and C-8 proton). The second metabolite is therefore identified as 7β-hydroxydihydrodrimenin (6a), with the absolute stereochemistry as indicated. It was later learned that 6a is a synthetic intermediate to some drimanic sesquiterpenes.[12] The synthetic and naturally occurring compounds 6a were identical as compared by tlc, ir, ^{1}Hmr, ms, and optical rotation.*

The third and most polar major component was a low melting solid (43-45°) with a molecular formula of $C_{15}H_{24}O_4$. Comparison of its ir, ^{1}Hmr, and mass spectra with those of 5 and 6a suggested that the third component is also a drimanic lactone. The ir spectrum shows an absorption at 1765 cm^{-1}; the mass spectrum has a strong $C_4H_5O_2$ peak; and the ^{1}Hmr spectrum (see Figure 4) exhibits multiplets at δ4.32 (2H), 3.16 (1H), and 2.26 (1H); all characteristic of the γ-lactone moiety in these compounds.

*The authentic sample was kindly provided by Professor E. Wenkert.

The mass spectrum does not however, show a $C_{10}H_{17}$ peak, but a $C_{10}H_{17}O$ peak, possibly due to a hydroxyl substituted fragment 17. Since the ^{1}Hmr spectrum displays three tertiary methyls, the hydroxyl group must be located at either C-1, C-2, C-3, or C-6. The ir spectrum shows hydroxyl absorption at 3580 and 3430 cm^{-1}, consistent with the above hypothesis. Assuming a dihydrodrimenin skeleton 22, the molecular formula dictates that the fourth oxygen is another hydroxyl group. The other hydroxyl function is not located at C-1 to C-6 since the $C_{10}H_{17}O$ mass fragment 17 contains only one oxygen. The $C_4H_5O_2$ lactone fragment and the ^{1}Hmr signals for the hydrogens at C-8 (δ3.16), C-9 (2.26), and C-12 (4.32) indicate that the additional hydroxyl group is not a part of the γ-lactone system. It is therefore located at C-7. The diol was assigned the structure 6α,7β-dihydroxydihydrodrimenin (7a), after characterization as its diacetate derivative 7b, as described below.



7a R = H

7b R = Ac

Treatment of the diol with acetic anhydride/pyridine gave a di-*O*-acetyl compound as shown by ms, ^{1}Hmr, and ir spectral data. The ^{1}Hmr spectrum (see Figure 5) shows that the two protons (δ3.88) geminal to hydroxyl groups in the diol have shifted downfield in the diacetate to δ5.57 and 5.15, now being geminal to *O*-acetyl groups. Each multiplet exists as a doublet of a doublet, *mutually coupled by 9Hz*.* The coupling constant is typical of vicinally coupled *trans*-diaxial protons. It was established earlier that in the diol, one hydroxyl group is at C-7. The diacetate derivative therefore has acetyl groups at C-7 and C-6, and in a diequatorial relationship. Thus the structure is assigned as 6α,7β-diacetoxydihydrodrimenin (*7b*). Although the absolute configuration of diol *7a* was not determined, biogenetic considerations suggest that the absolute configuration of *7a* is the same as the previous two metabolites, *5* and *6a*. The absolute structure of *7a* is then 6α,7β-dihydroxydihydrodrimenin.

Chemical conversion of the previously undescribed diol *7a* to drimenin (*24*) or isodrimenin (*25*) via compound *23* was attempted using activated titanium.[13] However,

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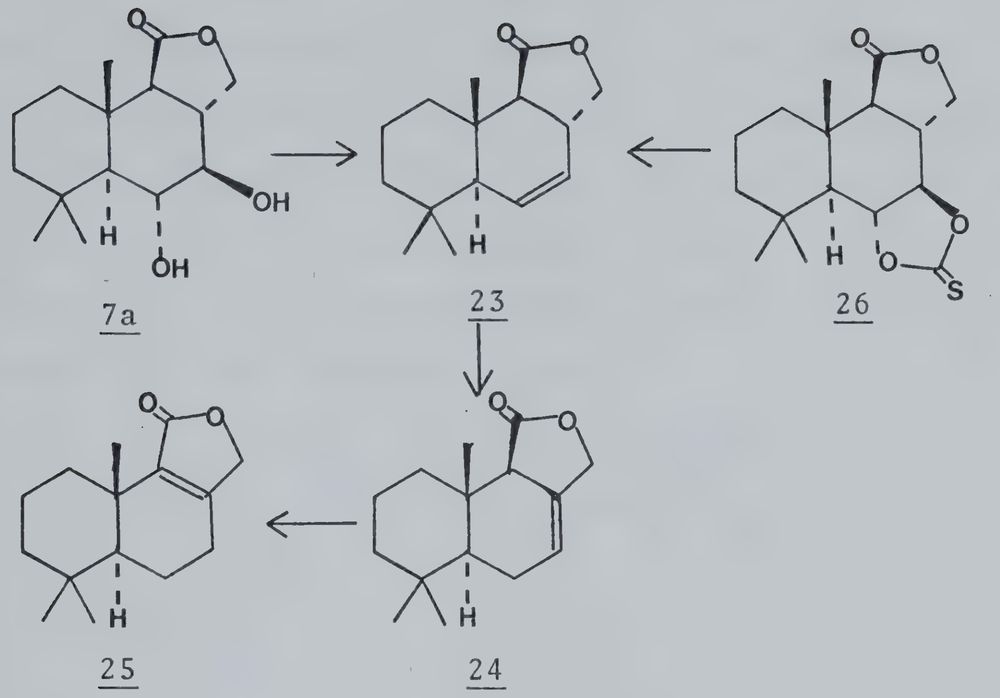
*All ^{1}Hmr assignments for diacetate *7b* are supported by the appropriate decoupling experiments.

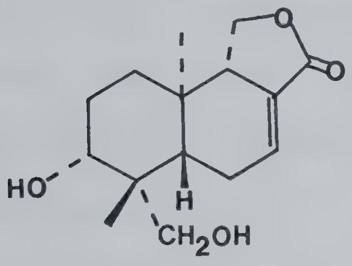


this was unsuccessful as neither 23, 24, nor 25 could be identified after the reaction. Reaction of 7a with *N*,*N'*-thiocarbonyldiimidazole yielded only unidentified products. Hence formation of 23 could not be attempted using this method. Due to the small amounts of diol 7a available, we were unable to pursue further reactions and hence a direct chemical correlation with a known compound could not be effected.

Sesquiterpenes of the bicyclofarnesane skeleton 18 are found predominantly in trees and shrubs,[11,15] however they are also known in tobacco,[9b,16] liverwort,[17] and water-pepper[18] plants. With the exception of a few metabolites of *Penicillium* fungi,[19] bicyclofarnesane sesquiterpenes are confined to higher plants. This is

only the third report of these rare fungal metabolites.

The bicyclofarnesane skeleton is present in most di- and triterpenes, however was not known in sesquiterpenes until 1954 when Djerassi and co-workers[20] discovered iresin (27), the long-sought after 'missing link' between lower and higher terpenes. However, iresin



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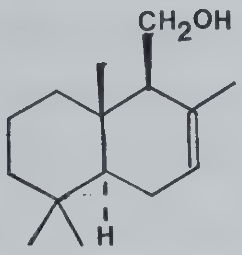

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possessed the opposite absolute configuration to the steroids and higher terpenes.[11a] The structure of drimenol (28) was elucidated by Brooks and Overton[21] in 1957 and constituted the first sesquiterpene containing both the skeletal structure and the absolute configuration of the higher terpenes. The biogenetic significance of this class of sesquiterpenes is further enhanced by our discovery of bicyclofarnesane sesquiterpenes, triterpenes, and steroids from the same source. Together with the dihydrodrimenin sesquiterpenes 5, 6a, and 7a, the culture broth of *M. reticulata* also yielded glochidone (8)[22] and β-sitosterol (9).

In addition to the above metabolites, chromatography of the neutral fraction also gave small quantities of aromatic compounds, all with the molecular formula $C_{22}H_{22}O$. Their ir spectra showed hydroxyl absorption. The ^{1}Hmr spectra of these compounds all exhibited methyl doublets (J = 7 Hz) at δ1.6 and the corresponding quartet at δ4.1 - 4.4. The aromatic protons observed occur in the region δ6.6 - 7.5. The uv spectrum of one compound shows a maximum at 276 nm while the other component shows a maximum at 285 with a shoulder at 306 nm. These aromatic components were not identified.

An examination of the acidic fraction from the culture broth of *M. reticulata* is presented below.

Preliminary separation of the components of the acidic fraction was carried out by column chromatography. Three main fractions 1, 2, and 3 respectively were examined in order of increasing polarity. From the least polar fraction 1, a small amount of crystals, mp 269-273° were isolated by recrystallization from acetone/pentane. High resolution ms indicated a molecular formula of $C_{15}H_{22}O_3$. The ir spectrum shows hydroxyl (3500, 2400-3300 cm^{-1}) and carbonyl (1740, 1715 cm^{-1}) absorptions. The ^{1}Hmr spectrum exhibits at least 5 methyl singlets (δ1.34, 1.08, 0.91, 0.86, and 0.85)

which is not compatible with the above molecular formula suggestive of a sesquiterpenoid. Chemical ionization (NH_3) ms gave an M+18 peak of 518, more compatible with the ^{1}Hmr and ir data.

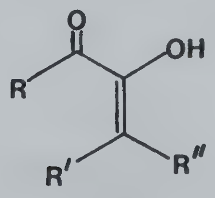
Treatment of the fraction 1 metabolite with excess diazomethane yielded a monomethyl ester triterpenoid with the molecular formula $C_{31}H_{46}O_6$. The ir spectrum shows carbonyl absorption (1735, 1700 cm^{-1}) and possibly hydroxyl absorption (3550 cm^{-1}). The ^{1}Hmr spectrum exhibits one methyl ester singlet and at least 5 tertiary methyl singlets. The ^{13}Cmr indicates a ketonic carbon (204.8 ppm) and an ester carbon (168.5 ppm). Attempts to acetylate the monomethyl ester with acetic anhydride/pyridine were unsuccessful.

Fraction 2 gave a precipitate which decomposed at 270-274°. The molecular formula $C_{30}H_{44}O_8$ was obtained by hrms. The ir spectrum shows hydroxyl absorption (3450, 2300-3300 cm^{-1}), and bands at 1735, 1705, and 1650 cm^{-1}. Separation of the components from this fraction was best achieved after esterification of fraction 2 with diazomethane. Preparative tlc of the esterified products yielded two compounds with molecular formulas $C_{16}H_{24}O_4$ and $C_{32}H_{48}O_8$.

The latter compound was recrystallized from methanol to give star-shaped crystals, mp 177-182°. The ir

spectrum shows bands at 3450, 1730, 1710, 1680, and 1655 cm^{-1}. A doublet of doublets (J = 13, 4 Hz) at δ4.35 in the ^{1}Hmr spectrum (see Figure 6) collapses to a doublet (J = 13 Hz) on D_2O exchange. Two methyl ester singlets at δ3.78 and 3.71 partially conceal a multiplet at δ3.7. A broad singlet appears at δ3.47 and methyl singlets at δ1.29, 1.20, 1.16 and 1.13(3). The uv spectrum shows a band at 278 nm.

Treatment of the dimethyl ester from fraction 2 with acetic anhydride/pyridine yielded the corresponding diacetate as shown by ms and ^{1}Hmr (see Figure 7). The original doublet of doublets at δ4.35 has now shifted downfield to a doublet at δ5.35 (J = 13 Hz). These observations can be accounted for by the presence of an allylic alcohol in the original metabolite. The ir spectrum appears to show some hydroxyl absorption (3550 cm^{-1}) together with bands at 1735, 1695, and 1665 cm^{-1}. The uv now absorbs at a shorter wavelength of 244 nm. The ir and uv data accumulated support a diosphenol structure 29 in the original metabolite.



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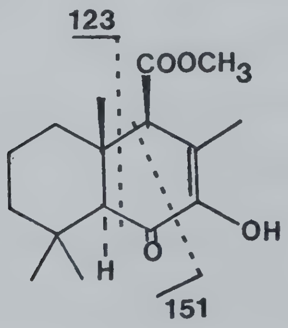
The $C_{16}H_{24}O_4$ compound isolated from the esterification of fraction 2 has ir absorption (3430, 1690, and 1660 cm^{-1}) characteristic of a diosphenol (see Figure 8). Moreover, the uv spectrum shows an absorption maximum at 273 nm, supporting this hypothesis. The ir spectrum also contains a 1735 cm^{-1} band, consistent with the methyl ester singlet (δ3.72) observed in the ^{1}Hmr spectrum (see Figure 9). The ^{1}Hmr spectrum exhibits 3 methyl singlets and a low field methyl doublet (δ1.80, J = 2 Hz) coupled* to a quartet at δ3.40 (1H, J = 2 Hz). After consideration of the spectral data, structure 10 is postulated. The δ1.80 doublet is assigned to the C-12 vinyl methyl which is coupled to the proton at C-9 (δ3.40). The mass spectrum of the compound contains the $C_{10}H_{15}O$ (m/e 151) and C_9H_{15} (m/e 123) fragments as indicated in structure 10. Acetylation of 10 was



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*^{1}Hmr decoupling studies confirm that the signals at δ3.40 and 1.80 are mutually coupled.

unsuccessful due to the small amount of the compound available.

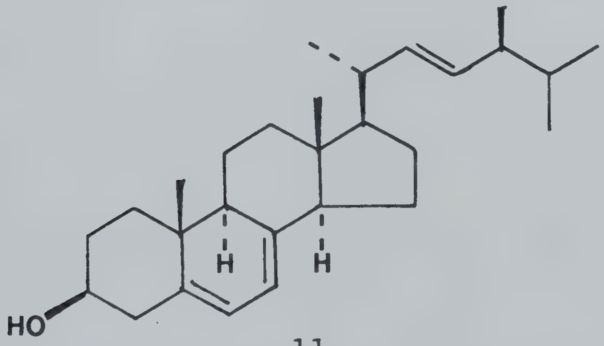
The most polar fraction 3 was subjected to ptlc. However, the components could not be separated cleanly. Treatment of fraction 3 with diazomethane, followed by ptlc enabled the purification of a small amount of triterpenoid diester with the molecular formula $C_{32}H_{48}O_8$. The ir spectrum shows hydroxyl (3510 cm^{-1}) and ester (1730 cm^{-1}) absorptions. The ^{1}Hmr spectrum exhibits two methyl ester singlets (δ3.68, 3.62) and several high field methyl signals as well as a doublet of doublets (J = 12, 6 Hz, d with D_2O exchange, J = 12 Hz) at δ4.66, a broad doublet at δ4.16 (J = 9 Hz, dq with D_2O exchange, J = 9, 2 Hz), a multiplet at δ3.07, and a broad singlet at δ2.61.

Treatment of the fraction 3 diester with acetic anhydride/pyridine gave a monoacetate derivative (ms, ^{1}Hmr) which shifted the δ4.66 signal downfield to δ5.55 (d, J = 13 Hz), indicative of an acetylation of an allylic alcohol. The ir spectrum shows hydroxyl absorption (3540 cm^{-1}) indicative of non-reactive alcohols such as tertiary alcohols, and ester absorption (1730 cm^{-1}).

The acidic metabolites described above have not been reported in the literature. It is interesting to

note that the two triterpenoid diesters ($C_{32}H_{48}O_8$) isolated have formula dimeric to the sesquiterpenoid monoester 10 ($C_{16}H_{24}O_4$). However, we cannot at this time suggest reasonable structures for these diesters. Due to the small amount of compounds available, further experiments were not possible.

The mycelia of *M. reticulata* were extracted with ethyl acetate and investigated only briefly. A small amount of solid crystallized from the crude mycelia extract and was identified (ir, ms) as ergosterol (11). The extract was separated into neutral and acidic fractions. The neutral fraction consisted of numerous components (tlc). The acidic fraction appeared simpler and was subjected to ptlc. However, appreciable quantities of identifiable compounds could not be isolated. The mycelia was not investigated further.



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EXPERIMENTAL

Mass spectra were recorded on an A.E.I. MS-50 mass spectrometer coupled to a DS 50 computer, or an A.E.I. MS-9 mass spectrometer (chemical ionization), and are reported as m/e (relative intensity). Unless diagnostically significant only peaks at least 20% as intense as the base peak are reported. Infrared spectra were recorded on a Unicam SP1000 or Perkin-Elmer Model 421 dual grating spectrophotometer, uv spectra on a Unicam SP1700 spectrophotometer, and optical rotations on a Perkin-Elmer Model 241 polarimeter. Proton magnetic resonance were measured on a Varian HA-100 spectrometer interfaced to a Digilab FTS/NMR-3 data system or a Bruker WP-60 spectrometer interfaced to a Nicolet 1080 computer with TMS as internal standard. Carbon magnetic resonance spectra were measured on a Bruker HFX-90 spectrometer interfaced to a Nicolet 1085 computer with TMS as internal standard. Melting points were recorded on a Thomas Model 40 micro hot stage or a Gallenkamp mp apparatus (sealed tube), and are uncorrected.

Preparative tlc was carried out on 0.75 mm layers of silica gel G (W. Merck, Darmstadt) containing 1% electronic phosphor (General Electric, Cleveland), and materials were detected by spraying with 30% sulfuric

acid and charring. Silica gel (Woelm, < 0.063 mm) was used for column chromatography. Skellysolve B refers to Skelly Oil Company light petroleum, bp 62-70°C.

Growth of *Mycocalia reticulata* on Liquid Medium and Isolation of the Crude Metabolites

The aqueous medium used for culture growth (Brodie liquid medium) has the following composition per litre: maltose, 5.0 g; dextrose, 2.0 g; yeast extract (Difco), 2.0 g; KH_2PO_4, 0.5 g; $Ca(NO_3)_2 \cdot 4H_2O$, 0.5 g; $MgSO_4$, 0.24 g; peptone, 0.2 g; asparagine, 0.2 g; $Fe_2(SO_4)_3$, trace; glycerol, 6 ml. The medium was autoclaved at 120°C for 20 minutes before use.

Agar slant tube cultures of *M. reticulata* (strain 5465)* were used to innoculate 500 ml Erlenmeyer flasks containing 200 ml of the above medium. These were allowed to mature at 25°C for at least 30 days. To initiate large scale growths the contents of one 500 ml Erlenmeyer were blended (Waring blender) and 10 ml portions of the resulting suspension were trans-

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*Cultures were obtained from Dr. H. Ginns, Biosystematics Research Institute, Agriculture Canada, Ottawa, Ontario.

ferred under sterile conditions to 4 ℓ Fernbach flasks containing 1 ℓ of the above liquid medium. After 30 days growth at 25°C, the mycelium was removed by filtration through cheesecloth and the culture broth was extracted with an equal volume of ethyl acetate in three portions. The ethyl acetate extract was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to provide the crude extract as a brown semi-solid (~0.2 g/ℓ of culture broth).

Isolation of Coumarin 13 or 14

The crude extract (2.4 g) was dissolved in 80% aqueous methanol and partitioned with Skellysolve B. The Skellysolve B layer was concentrated under reduced pressure to give a yellow liquid (93 mg). Preparative tlc ($CHCl_3$/PhH/CH_3OH, 10:10:1) gave the coumarin as an oil (1.5 mg, R_f 0.7).

UV(CH_3OH) λ_{max}: 220, 255, 290, 364 nm;
base: 256, 300, 364 nm.
IR($CHCl_3$): 3520, 1700, 1590, 1500, 1430, 1375, 1280, 1090, 990, 900 cm^{-1}.
^{1}HMR($CDCl_3$): δ7.62 (dd, 1, J = 8, 2 Hz, H-6), 7.55 (d, 1, J = 2 Hz, H-8), 6.92 (d, 1, J = 8 Hz, H-5), 5.48 (m, 1, $W_{\frac{1}{2}}$ = 14 Hz, CH-C$\underline{H}$=C$(CH_3)_2$), 4.52 (bd, 2, J = 7 Hz,

$C\underline{H}_2-CH=C(CH_3)_2$), 3.88 (s, 3, OCH_3), 1.80, 1.76 (bs, 3 each, $CH_2-CH=C(C\underline{H}_3)_2$).

MS: m/e calcd. for $C_{15}H_{16}O_5$: 276.0998, found: 276.1006.

Preliminary Isolation of Drimanes 5, 6a, and 7a

A methylene chloride solution of the crude extract (1.5 g) was separated into acidic and neutral compounds by extraction with cold 5% aqueous NaOH. The neutral fraction (0.2 g) was subjected to ptlc (PhH/acetone/HOAc, 75:25:1) to give nearly pure metabolites 5 (5 mg, R_f 0.78), 6a (22 mg, R_f 0.55), and 7a (44 mg, R_f 0.47).

7-Ketodihydrodrimenin, 5

The least polar metabolite was recrystallized from Skellysolve B to give 5 as needles, mp 120-122°; $[\alpha]_D^{25}$ -118° (c 0.002 benzene).

IR($CHCl_3$): 1770, 1715, 1455, 1390, 1370, 1160, 1040 cm^{-1}.

$^1HMR(CDCl_3)$: δ4.45 (m, 2, $W_{\frac{1}{2}}$ = 15 Hz, H-12), 3.28 (m, 1, $W_{\frac{1}{2}}$ = 30 Hz, H-8), 2.70 (d, 1, J = 12.5 Hz, H-9), 2.48 (m, 1, $W_{\frac{1}{2}}$ = 18 Hz, H-1β),* 2.45 (m, 2, $W_{\frac{1}{2}}$ = 16 Hz, H-6),

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[*] This signal is partially hidden by the 4-line multiplet centered at δ2.45 (H-6). However, in the spectrum in C_6D_6 the H-6 signal is shifted upfield by 0.3 ppm, exposing the H-1β signal which appears as a doublet of double doublets (J = 11, 4, 2 Hz). The low field position of the H-1β signal is presumably caused by the deshielding effect of the C-11 carbonyl and is well documented in the steroid field.[23]

1.75 (m, 1, $W_{\frac{1}{2}}$ = 20 Hz, H-5), 0.91 (s, 6, CH_3), 0.85 (s, 3, CH_3).

^{13}CMR($CDCl_3$): 66.4, 53.6, 48.8, 44.8, 41.6, 39.6, 36.7, 33.5, 32.5, 21.3, 18.1, 15.1 ppm.

(The C-7 and C-11 carbonyl carbons and presumably a quaternary carbon (C-4 or C-10) were not detected due to the small amount of sample).

MS: m/e calcd. for $C_{15}H_{22}O_3$: 250.1569, found: 250.1569(8), 235(7), 194(46), 166(11), 137(11), 122(67), 109(21), 85(100), 69(25).

Metabolite 5 is identical (tlc, ir, ^{1}Hmr, ms, optical rotation, mp, mmp) with an authentic sample of 7-ketodihydrodrimenin.[11d]

7β-Hydroxydihydrodrimenin, 6a

Compound 6a was recrystallized from benzene/pentane to give fine needles, mp 157-158° (sealed tube), $[\alpha]_D^{25}$ -65° (c 0.0024, benzene).

IR($CHCl_3$): 3610, 3520, 1765, 1470, 1395, 1370, 1340, 1055, 1040, 1020 cm^{-1}.

^{1}HMR($CDCl_3$): δ4.29 (m, 2, $W_{\frac{1}{2}}$ = 17 Hz, H-12), 4.11 (m, 1, $W_{\frac{1}{2}}$ = 26 Hz, H-7), 3.01 (m, 1, $W_{\frac{1}{2}}$ = 37 Hz, H-8), 2.23 (d, 1, J = 8.5 Hz, H-9), 2.17 (m, 1, H-1β),

1.82 (apparent ddd, 1, J = 13 Hz, 6, 2 Hz, H-5), 1.06 (s, 3, CH_3), 0.93 (s, 3, CH_3), 0.88 (s, 3, CH_3).

^{13}CMR($CDCl_3$): 197.5 (s, C-11), 69.4 (d, C-7; t, C-12), 54.9 (t), 50.2 (d, C-8), 41.3 (t), 40.8 (d, C-9; t), 36.3 (s), 33.3 (d, C-5; s), 27.1 (t, C-2), 22.0 (q), 18.0 (q), 16.9 (q) ppm.

MS: m/e calcd. for $C_{15}H_{24}O_3$: 252.1726,

found: 252.1708(10), 237(21), 234(20), 219(20), 196(80), 178(84), 167(29), 137(70), 124(40), 123(58), 119(27), 109(55), 107(22), 105(20), 95(37), 93(25), 91(27), 85(100), 81(48), 79(28), 77(20), 69(48), 67(30), 55(45).

Metabolite 6a is identical (tlc, ir, ^{1}Hmr, ms, and optical rotation) with authentic 7β-hydroxydihydrodrimenin.[12]

6α,7β-Dihydroxydihydrodrimenin, 7a

The most polar ptlc component was chromatographed (PhH/acetone/HOAc, 75:25:1) again to give crystalline 7a, mp 43-45°.

IR($CHCl_3$): 3580, 3430, 1765, 1465, 1390, 1370, 1335, 1070, 1020 cm^{-1}.

^{1}HMR($CDCl_3$): δ4.32 (m, 2, $W_{\frac{1}{2}}$ = 22 Hz, H-12), 3.88 (m, 2, $W_{\frac{1}{2}}$ = 13 Hz, H-6, H-7), 3.16 (m, 1, $W_{\frac{1}{2}}$ = 37 Hz, H-8), 2.26 (d, 1, J = 8.5 Hz, H-9), 2.15 (m, 1, H-1β), 1.19 (s, 3, CH_3), 1.10 (s, 6, CH_3).

MS: m/e calcd. for $C_{15}H_{24}O_4$: 268.1675, found: 268.1668(6), 253(7), 250(13), 239(20), 235(15), 185(47), 166(70), 153(100), 110(63), 109(40), 107(31), 97(53), 95(26), 93(37), 91(29), 85(52), 81(40), 79(31), 77(24), 69(54), 67(32), 57(20), 55(53), 53(22).

Diol 7a was further characterized as its diacetate derivative 7b.

7β-Acetoxydihydrodrimenin, 6b

A solution of alcohol 6a (2.7 mg) in pyridine (0.1 ml) and acetic anhydride (0.1 ml) was allowed to stand at room temperature for 1 day and then was poured into water and was extracted with ether (3x). The combined ethereal extracts were washed with water (2x), dried ($MgSO_4$), and concentrated under reduced pressure to give crude acetate (2.8 mg). Purification by ptlc (PhH/acetone/HOAc, 75:25:1) yielded 6b as an oil.

IR($CHCl_3$): 1770, 1740, 1470, 1385, 1370, 1335, 1260, 1135, 1025 cm^{-1}.
^{1}HMR($CDCl_3$): δ5.12 (m, 1, $W_{\frac{1}{2}}$ = 26 Hz, H-7), 4.21 (m, 2, $W_{\frac{1}{2}}$ = 12 Hz, H-12), 3.10 (m, 1, $W_{\frac{1}{2}}$ = 37 Hz, H-8), 2.28 (d, 1, J = 8.5 Hz, H-9), 2.09 (m, 1, H-1β), 2.06 (s, 3, OAc), 1.90 (apparent ddd, 1, J = 13, 6, 2 Hz, H-5), 1.08 (s, 3, CH_3), 0.94 (s, 3, CH_3), 0.88 (s, 3, CH_3).
MS: m/e calcd. for $C_{17}H_{26}O_4$: 294.1831, found: 294.1835(4), 279(3), 234(100), 219(71), 178(89), 137(7), 123(23), 119(32), 109(33), 107(26), 105(32), 95(21), 93(31), 91(32), 85(44), 81(35), 79(26), 69(53), 67(22), 55(41).

6α,7β-Diacetoxydihydrodrimenin, 7b

Acetylation of diol 7a (30 mg) was performed as described for 6a, followed by ptlc (PhH/acetone/HOAc, 75:25:1) to give diacetate 7b as an oil (15 mg) which partially solidified after several weeks. Recrystallization from cyclohexane/Skellysolve B yielded 7b as needles, mp 122-123°; $[\alpha]_D^{25}$ -66° (c 0.016, benzene).
IR($CHCl_3$): 1770, 1745, 1470, 1370, 1345, 1270, 1140, 1040 cm^{-1}.

^{1}HMR(CDCl$_3$): δ5.51 (dd, 1, J = 11.5, 9 Hz, H-6), 5.15 (dd, 1, J = 9, 9 Hz, H-7), 4.24 (m, 2, $W_{\frac{1}{2}}$ = 14 Hz, H-12), 3.26 (m, 1, $W_{\frac{1}{2}}$ = 37 Hz, H-8), 2.33 (d, 1, J = 9 Hz, H-9), 2.15 (m, 1, H-1β), 2.04 (s, 3, OAc), 2.02 (s, 3, OAc), 1.41 (d, 1, J = 11.5 Hz, H-5), 1.20 (s, 3, CH$_3$), 1.05 (s, 3, CH$_3$), 0.94 (s, 3, CH$_3$).

^{13}CMR(CDCl$_3$): 176.1 (s, O$\underline{C}$OCH$_3$), 169.9 (s, O$\underline{C}$OCH$_3$), 74.4 (d, C-7), 70.2 (d, C-6), 68.3 (t, C-12), 53.2 (d, C-8(C-5)), 52.9 (d, C-5(C-8)), 43.5 (t), 41.0 (t), 38.4 (s), 37.6 (d, C-9), 36.1 (t, C-2), 33.3 (s), 22.3 (q), 21.4 (q), 20.5 (q), 17.7 (q), 17.6 (q) ppm. The C-11 carbonyl carbon was not detected due to the small amount of sample.)

MS: m/e calcd. for $C_{19}H_{28}O_6$: 352.1886, found: 352.1882(5), 292(14), 250(29), 235(15), 232(100), 217(17), 195(10), 153(30), 149(23), 85(22), 82(33), 69(43), 55(33).

ANALYSIS: calcd. for $C_{19}H_{28}O_6$: C 64.75, H 8.01; found: C 64.33, H 8.10.

Jones' Oxidation of 7β-hydroxydihydrodrimenin, 6a

A solution of 6a (2.0 mg) in acetone (0.5 ml) was stirred at room temperature and excess Jones' reagent (1 drop) was added. This was followed by addition of

2-propanol to destroy excess reagent. Solid $NaHCO_3$ was then added and the mixture stirred for a few minutes. Filtration through charcoal and removal of the solvents under reduced pressure gave a crystalline product (1.8 mg) which was shown to be identical with ketone 5 by comparison of tlc, ir, ^{1}Hmr, and ms data.

Treatment of 6α,7β-Dihydroxydihydrodrimenin, 7a with activated Titanium[13]

To a stirred suspension of anhydrous titanium trichloride (49 mg, 0.32 mmole) in anhydrous DME (8 ml) under nitrogen was added lithium (8 mg, 1.1 mmole). After refluxing for 1 h, titanium was obtained as a fine black powder. To this stirred suspension was added diol 7a (~9 mg, 0.034 mmole) in anhydrous DME (4 ml). After stirring at room temperature for 1 h, the mixture was refluxed for 12 h and cooled. Ether was added and the mixture was filtered through a pad of Florisil. The filtrate was then concentrated under reduced pressure to give a yellow oil (10 mg). Infrared and ^{1}Hmr spectra, as well as tlc show some starting diol 7a present plus some higher R_f material. Preparative tlc (PhH/acetone/HOAc, 75:25:1) gave no identifiable material.

Treatment of 6α,7β-Dihydroxydihydrodrimenin, 7a with N,N'-thiocarbonyldiimidazole[14]

A solution of diol 7a (45 mg, 0.17 mmole) and N,N'-thiocarbonyldiimidazole (55 mg, 0.28 mmole) in dry benzene (6 ml) was refluxed for 16 h, after which time tlc showed no reaction. The solvent was removed under reduced pressure and additional N,N'-thiocarbonyldiimidazole (40 mg, 0.20 mmole) was added to the residue. A solution of these materials in dry diglyme was heated at 140° for 3 h and then poured into water and ether. The ethereal layer was washed with water, 1 N HCl, water, saturated $NaHCO_3$ solution, and water; dried ($MgSO_4$); and concentrated under reduced pressure to give a brown colored oil (40 mg) which appeared (tlc) to be mainly the starting diol 4a. None of the desired thiocarbonate 26 was detected by ms.

Isolation of $C_{22}H_{22}O$ Metabolites, Glochidone (8), and β-Sitosterol (9)

The crude extract was separated into neutral and acidic fractions as described above. Column chromatography of the neutral fraction (0.4 g) employing gradient elution ($CHCl_3$ to $CHCl_3/CH_3OH$) gave in the early fractions components less polar than metabolites 5, 6a, or 7a.

Preparative tlc ($CHCl_3/CH_3OH$, 50:1) of one fraction gave three components: R_f 0.75 (3 mg), R_f 0.70 (5 mg), and R_f 0.55 (3 mg).

The aromatic component at R_f 0.75 gave the following spectral data.

UV(CH_3OH) λ_{max}: 276 nm.

IR($CHCl_3$): 3600, 3550, 3360, 1600, 1500, 1455, 1375, 1330, 1290, 1110, 850 cm^{-1}.

^{1}HMR($CDCl_3$): δ6.7-7.4 (m), 4.36 (q, J = 7 Hz), 1.63 (d, J = 7 Hz).

MS: m/e calcd. for $C_{22}H_{22}O$: 302.1671, found: 302.1677(27), 287(44), 198(57), 183(100), 165(28).

The aromatic component at R_f 0.70 gave the following spectral data.

UV(CH_3OH) λ_{max}: 285, 306(sh) nm.

IR($CHCl_3$): 3600, 3550, 3360, 1600, 1500, 1455, 1375, 1330, 1120, 910, 900 cm^{-1}.

^{1}HMR($CDCl_3$): δ7.1-7.5 (m), 6.95 (dd, J = 8, 2 Hz), 6.65 (d, J = 8 Hz), 4.31 (q, J = 7 Hz), 4.10 (q, J = 7 Hz), 1.61 (d, J = 7 Hz), 1.59 (d, J = 7 Hz).

MS: m/e 302(53), 287(100), 209(20), 105(37).

The component at R_f 0.55 was identified as glochidone (8)[22] by comparison (tlc, ir, ^{1}Hmr, ms) with an authentic sample.*

Another slightly more polar fraction was also subjected to ptlc (pentane/acetone, 4:1) to give a solid material (19 mg), R_f 0.7, which was recrystallized twice from Skellysolve B to give β-sitosterol (9), identified by comparison (tlc, ir, ^{1}Hmr, ms) with an authentic sample.

Preliminary separation of the acidic fraction

Column chromatography (PhH/acetone/HOAc, 80:20:1) of the acidic fraction (0.52 g, see the preliminary isolation of 5, 6a, and 7a) gave three fractions in order of increasing polarity: fraction 1 (20 mg, R_f 0.7-0.8), fraction 2 (250 mg, R_f 0.6), and fraction 3 (60 mg, R_f 0.5), (PhH/acetone/HOAc, 75:25:1).

Isolation of the Metabolite from Fraction 1 and Esterification with Diazomethane

Recrystallization of the least polar fraction 1 from acetone/pentane gave crystals (~4 mg), mp 269-273°. IR($CHCl_3$): 3500, 2400-3400, 1740, 1715(sh), 1470, 1390, 1365, 1335, 1315, 1075, 965 cm^{-1}.

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*The authentic sample was kindly provided by Dr. W.H. Hui.

^{1}HMR($CDCl_3$): δ1.32, 1.08, 0.91, 0.86, 0.84 (s, CH_3). Chemical Ionization (NH_3) MS shows the M + 18 (m/e 518) peak.

MS: m/e calcd. for $C_{15}H_{22}O_3$: 250.1569,
found: 250.1567(16), 232(22), 219(19), 123(100), 91(20), 84(25), 81(35), 69(94), 67(29), 55(43).

To a stirred solution of the above metabolite (~11 mg) in CH_2Cl_2 was added 0.5 N diazomethane (0.5 ml) in CH_2Cl_2. The yellow solution was stirred at room temperature for 2 h and then concentrated under reduced pressure to give a white solid (8 mg), homogeneous by tlc (PhH/acetone/HOAc, 75:25:1), R_f 0.9.

IR($CHCl_3$): 3550*, 1730, 1700(sh), 1470, 1395, 1370, 1340, 1320, 1295, 1115, 1085, 990, 975, 955 cm^{-1}.

^{1}HMR($CDCl_3$): δ4.88 (bs, 1), 3.60 (s, 3, $COOCH_3$), 1.31, 1.06, 0.90 (s, 3 each, CH_3), 0.87 (s, 6, CH_3), 0.84 (s, 3, CH_3).

^{13}CMR($CDCl_3$): 204.8, 168.5, 106.3, 102.8, 81.1, 60.3, 60.2, 56.2, 55.4, 51.0, 48.9, 41.5, 41.3, 39.6, 38.9, 38.0, 36.3, 36.0, 33.9, 33.1, 32.9, 29.8, 29.7, 26.1, 21.6, 20.7, 19.2, 18.6, 18.1, 15.0, 13.7 ppm.

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*This absorption was very weak.

MS: m/e calcd. for $C_{31}H_{46}O_6$: 514.3295,
found: 514.3292(6), 499(2), 470(11), 455(3), 438(24), 252(46), 219(100), 162(24), 123(31), 119(22), 109(33), 107(45), 105(33), 95(28), 93(28), 91(35), 81(31), 69(42), 67(33), 55(38).

Isolation of Metabolites from Fraction 2 including 4,4,8,10β-Tetramethyl-9β-carbomethoxy-7-hydroxy-7-octal-6-one, 10

Fraction 2 yielded a small amount of precipitate which decomposed at 270-274°.

IR($CHCl_3$): 3450, 2300-3300, 1735(sh), 1705, 1650, 1455, 1385 cm^{-1}.

^{1}HMR($CDCl_3$): δ4.38 (d, J = 12 Hz), 3.48 (bs), 1.32, 1.20, 1.17, 1.14, 1.11 (s, CH_3).

MS: m/e calcd. for $C_{30}H_{44}O_8$: 532.3036,
found: 532.3063(10), 514(24), 496(22), 278(82), 266(24), 236(26), 219(28), 151(33), 123(50), 109(58), 95(26), 93(24), 81(45), 69(100), 55(51).

Esterification of fraction 2 (70 mg) with excess diazomethane (as described for fraction 1) and subsequent ptlc (pentane/ether, 3:1, double elution) gave components at R_f 0.8 (2 mg) and R_f 0.4 (5 mg). The latter component was recrystallized from methanol to give a diester as

white star-shaped crystals (2 mg), mp 177-182°.

UV(CH_3OH) λ_{max}: 278 nm.

IR($CHCl_3$): 3450, 1730, 1710, 1680, 1655, 1465, 1390(sh), 1380, 1355, 1330, 1120, 1105, 1015, 1000, 975 cm^{-1}.

^{1}HMR($CDCl_3$): δ4.35 (bdd, J = 12, 4 Hz, bd with D_2O exchange, J = 12 Hz), 3.78, 3.71 (s, 3 each, $COOCH_3$), 3.7 (m), 3.47 (bs), 2.88 (m), 1.29, 1.20, 1.16, 1.13 (CH_3).

MS: m/e calcd. for $C_{32}H_{48}O_8$: 560.3349,

found: 560.3335(24), 542(10), 528(100), 524(12), 513(25), 510(76), 496(49), 478(54), 292(61), 191(21), 123(29), 109(25), 81(26), 69(33), 55(25).

The component at R_f 0.8 was tentatively assigned structure 10.

UV(CH_3OH) λ_{max}: 273 nm.

IR($CHCl_3$): 3430, 1735, 1685, 1660, 1465, 1390, 1360, 1340, 1320, 1285, 1115, 1090, 1010 cm^{-1}.

^{1}HMR($CDCl_3$): δ3.72 (s, 3, $COOCH_3$), 3.40 (q, 1, J = 2 Hz, H-9), 2.12 (bs, 1, H-5), 1.80 (d, 3, J = 2 Hz, H-12), 1.18, 1.16, 1.10 (s, 3 each, CH_3).

MS: m/e calcd. for $C_{16}H_{24}O_4$: 280.1675,

found: 280.1678(50), 248(22), 221(20), 151(37), 123(53), 117(23), 111(23), 109(60), 97(30), 95(33),

91(23), 85(43), 83(39), 81(54), 79(22), 71(61), 69(94), 67(35), 57(100), 55(83).

Acetylation of the Diester from Fraction 2

The diester (1 mg) from fraction 2 (R_f 0.4) was dissolved in pyridine (0.5 ml) and acetic anhydride (0.25 ml) was added. The resulting solution was allowed to stand at room temperature for 1 day and then poured into water and extracted with ether (2x). The combined ethereal extracts were then washed with water (2x), dried ($MgSO_4$), and solvents removed under reduced pressure to give a yellow oil.

UV(CH_3OH) λ_{max}: 244 nm.

IR($CHCl_3$): 2500-3600 *, 1730, 1695, 1465, 1445, 1395, 1375, 1350(sh), 1100, 1010 cm^{-1}.

^{1}HMR($CDCl_3$): δ5.35 (bd, J = 13 Hz), 3.75, 3.74 (s, 3 each, $COOCH_3$), 3.7 (m), 2.84 (m), 2.27, 2.15 (s, 3 each, OAc), 1.35, 1.18, 1.14, 1.12, 1.01, 0.96 (CH_3).

Chemical Ionization (NH_3) MS shows the M + 18 (m/e 662) peak.

MS: m/e calcd. for $C_{34}H_{50}O_9$: 602.3455,

found: 602.3427(21), 570(100), 542(15), 510(33), 292(41), 250(23), 191(23), 137(25), 123(26), 109(32), 95(24), 81(36), 69(50), 57(39), 55(47).

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* This absorption was very weak.

Purification of Fraction 3 by Esterification with Diazomethane

Preparative tlc (PhH/acetone/HOAc, 75:25:1) of fraction 3 (60 mg) gave an impure white solid (29 mg, R_f 0.5). Esterification of the solid with excess diazomethane (as described for fraction 1) followed by ptlc (PhH/acetone/HOAc, 75:25:1) gave an oil, R_f 0.9 which was further purified by ptlc (pentane/ether, 2:1) to give a diester as a colorless oil (2 mg).

IR($CHCl_3$): 3500, 1730, 1460, 1390, 1370, 1350, 1090, 1000 cm^{-1}.

^{1}HMR($CDCl_3$): δ4.66 (dd, J = 12, 6 Hz, d with D_2O exchange, J = 12 Hz), 4.16 (bd, J = 9 Hz, dq with D_2O exchange, J = 9, 2 Hz), 3.68, 3.62 (s, 3 each, $COOCH_3$), 3.07 (bs), 2.62 (bs), 1.45, 1.40, 1.35, 1.17, 1.14, 1.10, 1.06, 0.99 (CH_3).

MS: m/e calcd. for $C_{32}H_{48}O_8$: 560.3349,
found: 560.3361(62), 542(38), 528(27), 524(38), 510(12), 294(31), 252(23), 220(24), 219(26), 151(25), 137(25), 128(21), 123(70), 109(56), 107(25), 105(24), 95(37), 93(28), 91(32), 83(21), 81(57), 79(53), 69(100), 67(38), 57(22), 55(71).

Acetylation of the Diester from Fraction 3

The diester (1.5 mg) from fraction 3 was acetylated with acetic anhydride/pyridine (as described for fraction

2) to give an oil (0.5 mg) homogeneous by tlc (PhH/acetone/HOAc, 75:25:1), R_f 0.85.

IR($CHCl_3$): 3540, 1730, 1450, 1425, 1385, 1365, 1340, 1190, 1080, 1010, 985 cm^{-1}.

^{1}HMR($CDCl_3$): δ5.55 (d, J = 13 Hz), 4.13 (dq, J = 9, 2 Hz), 3.68, 3.61 (s, 3 each, $COOCH_3$), 3.05 (bs), 2.61 (bs), 2.17 (s, 3, OAc), 1.14, 1.10, 1.04, 0.97, 0.95 (CH_3).

MS: m/e calcd. for $C_{34}H_{50}O_9$: 602.3455,

found: 602.3434(3), 584(5), 542(7), 524(12), 260(20), 252(15), 247(14), 234(43), 219(31), 165(29), 128(25), 123(52), 109(37), 107(22), 105(25), 95(29), 93(24), 91(26), 83(24), 81(42), 79(26), 77(21), 69(100), 67(31), 57(46), 55(70), 53(21).

Extraction of the Mycelia of *M. reticulata* and the Isolation of Ergosterol (11)

The mycelia of *M. reticulata* were extracted with ethyl acetate for 3 days in a Soxhlet apparatus. The ethyl acetate extract was then washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to give the crude mycelia extract as a dark brown oil. A small amount of solid crystallized from the crude extract. This was identified as ergosterol by comparison of its ir and ms with an authentic sample.

A methylene chloride solution of the crude mycelia extract (1.5 g) was separated into acidic (0.69 g) and neutral (0.36 g) compounds by extraction with cold 5% aqueous NaOH. Preparative tlc (PhH/acetone/HOAc, 75:25:1) of the acidic fraction (180 mg) did not yield appreciable quantities of identifiable compounds.

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APPENDIX

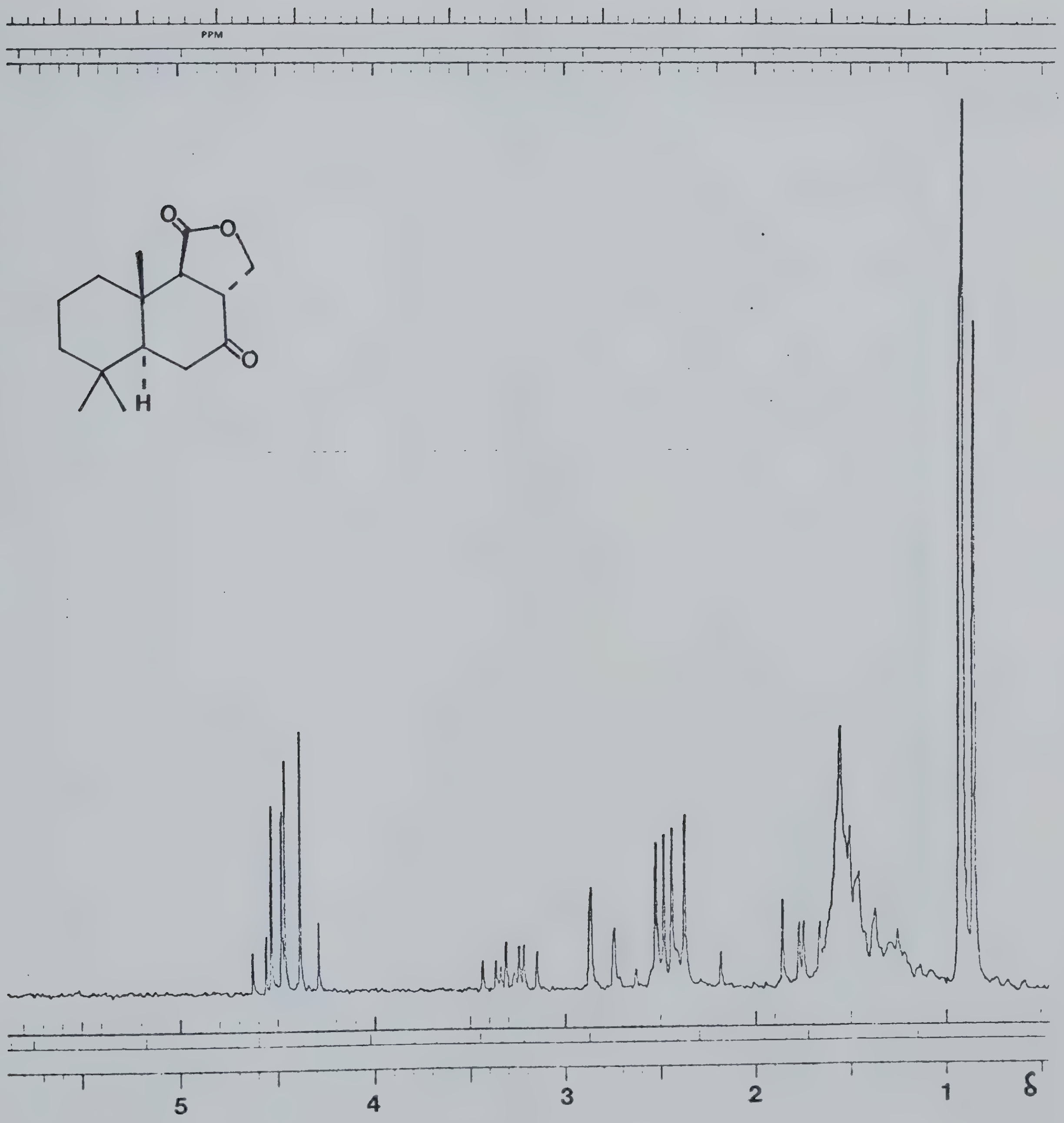


Figure 1. The ^{1}Hmr spectrum of 5.

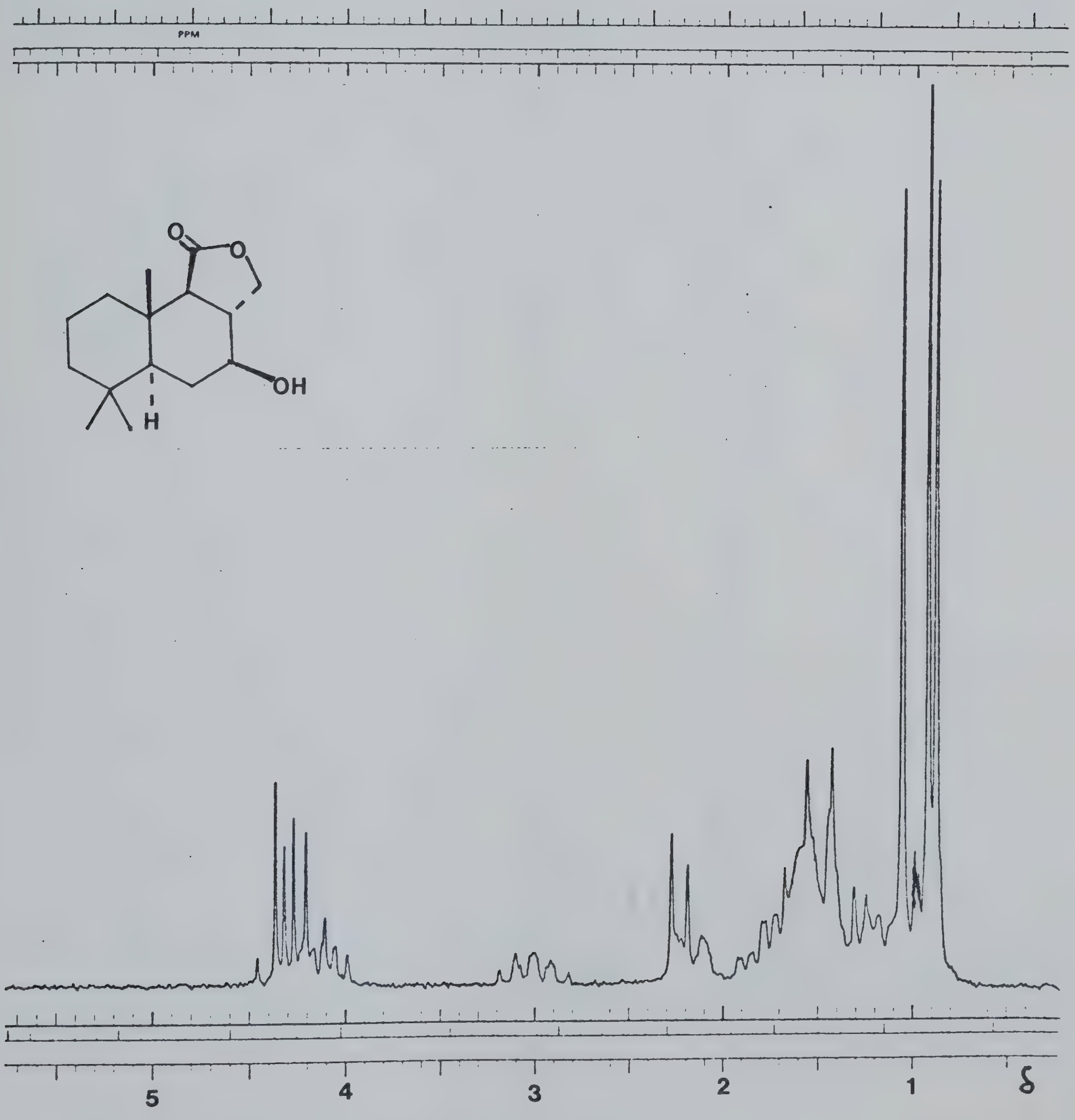


Figure 2. The ^{1}Hmr spectrum of 6a.

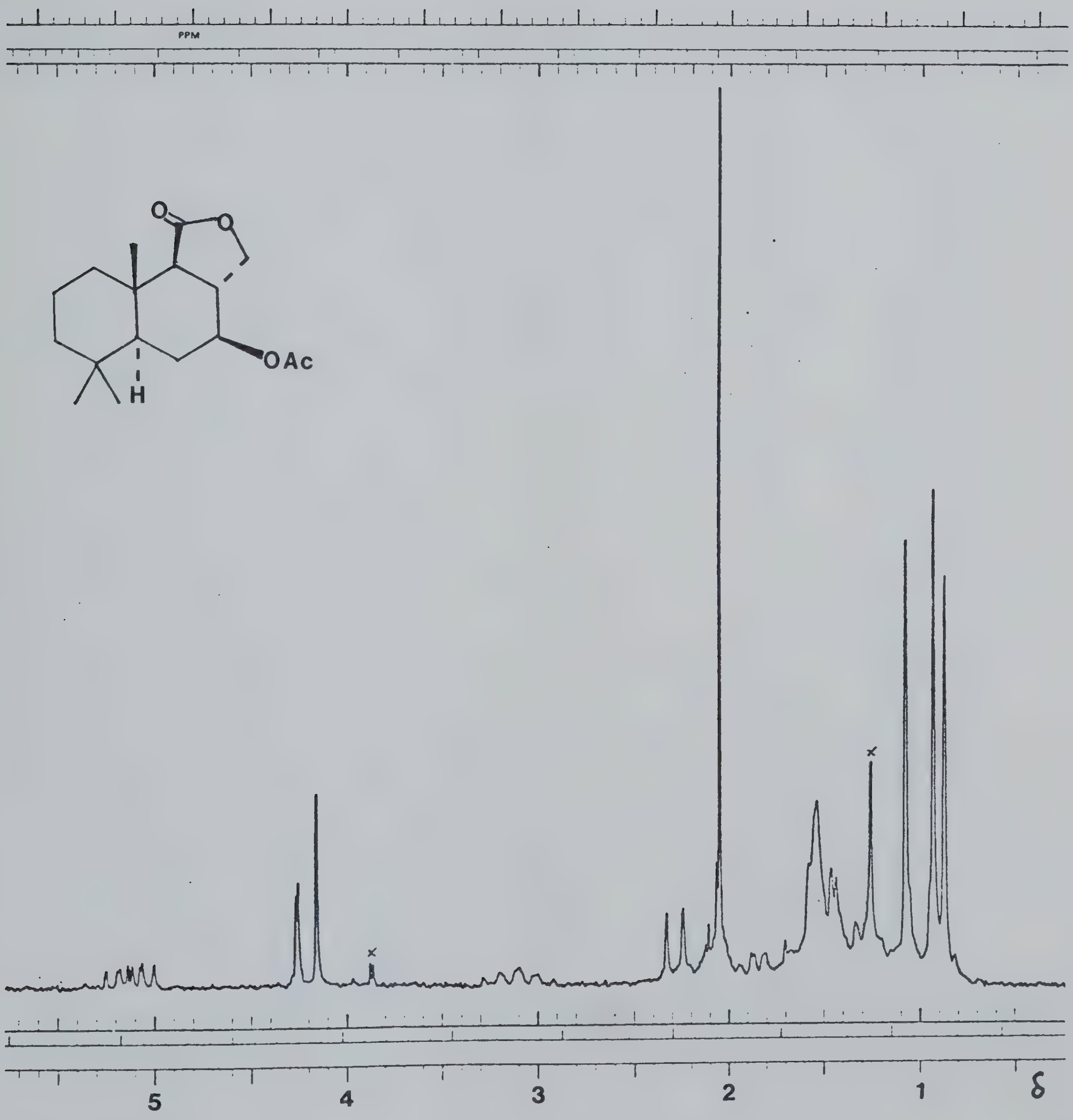


Figure 3. The ^{1}Hmr spectrum of 6b.

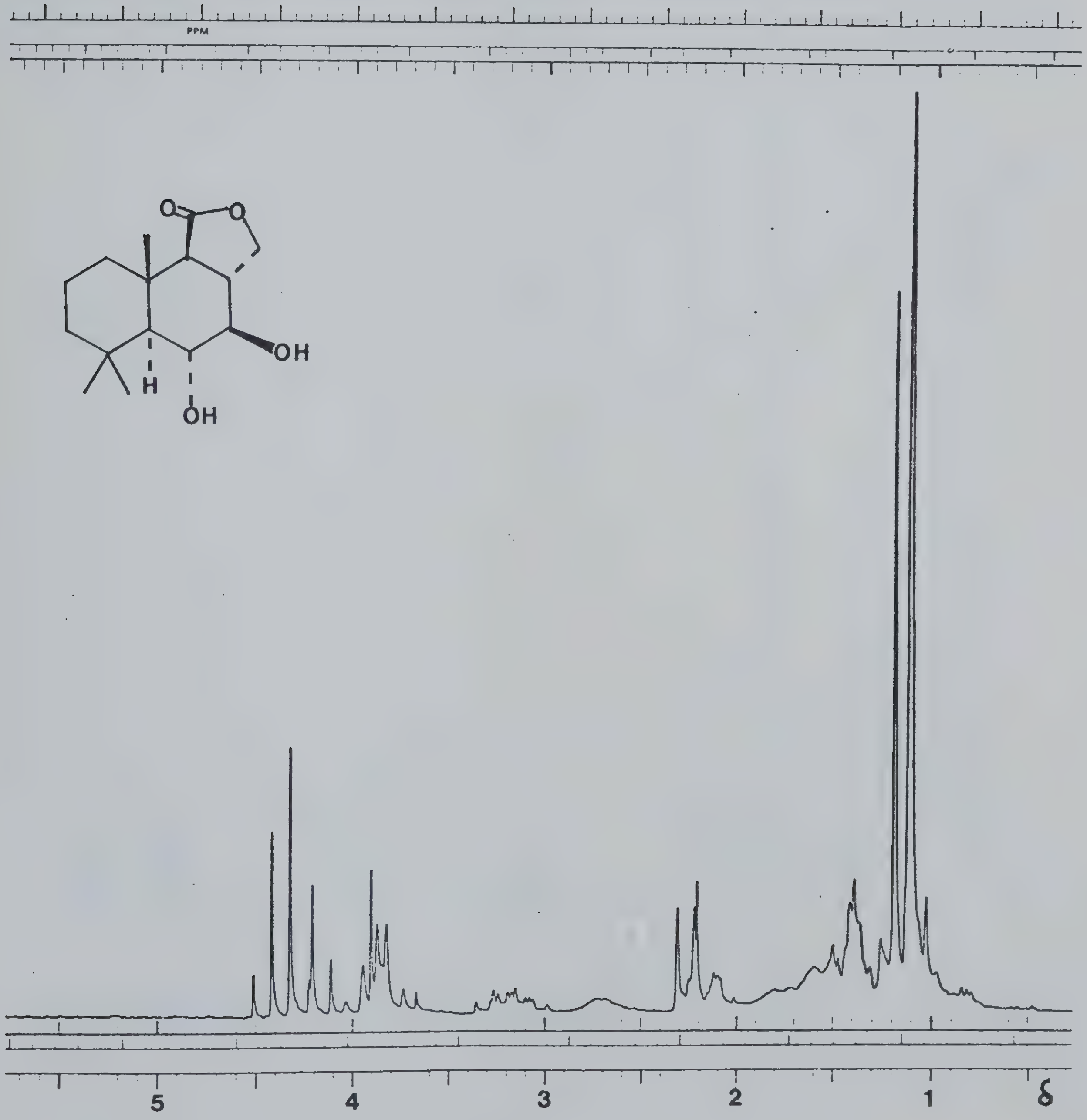


Figure 4. The ^{1}Hmr spectrum of 7a.

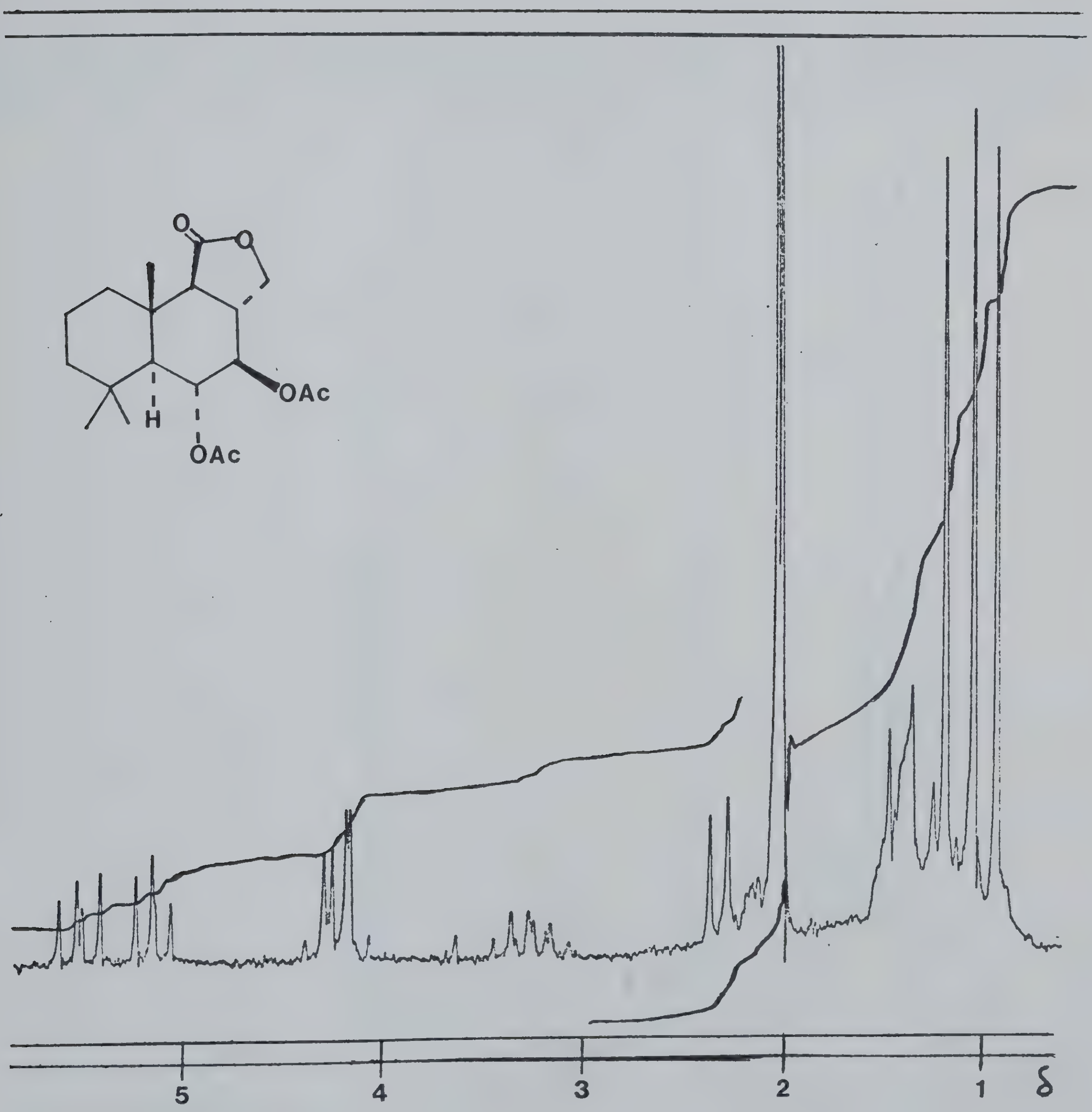


Figure 5. The ^{1}Hmr spectrum of 7b.

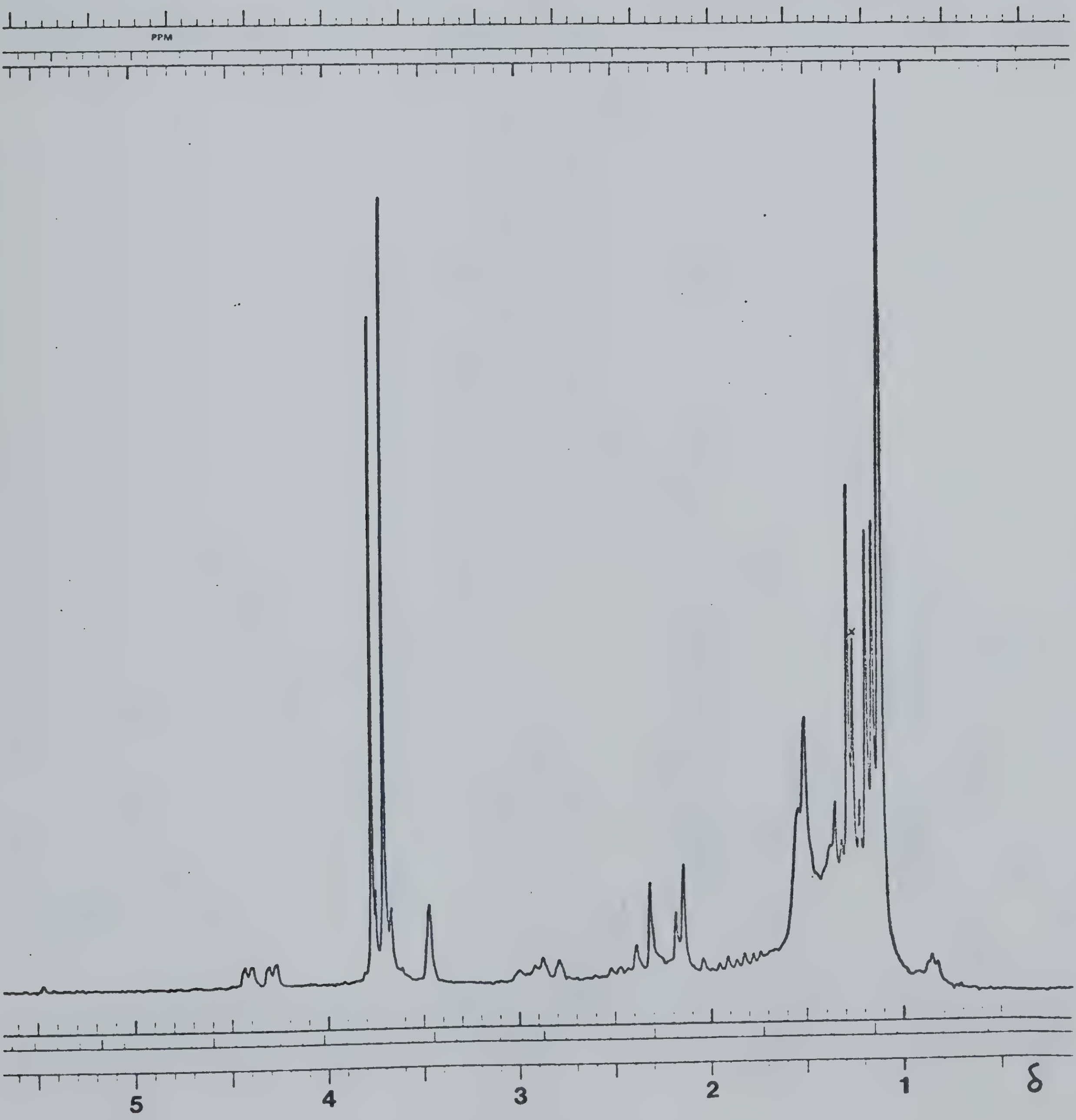


Figure 6. The ^{1}Hmr spectrum of the fraction 2 triterpenoid.

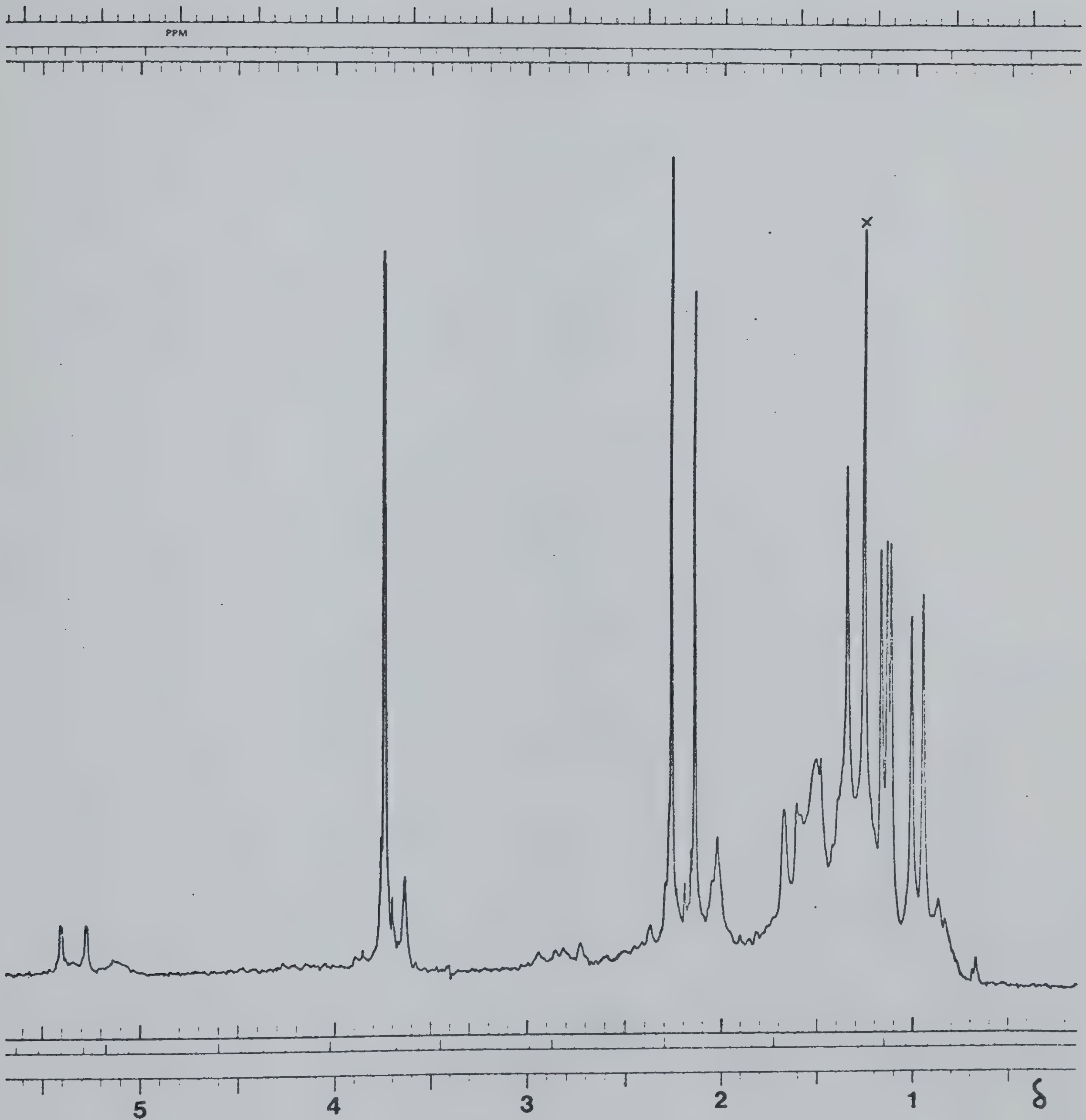


Figure 7. The ^{1}Hmr spectrum of the fraction 2 diacetate.

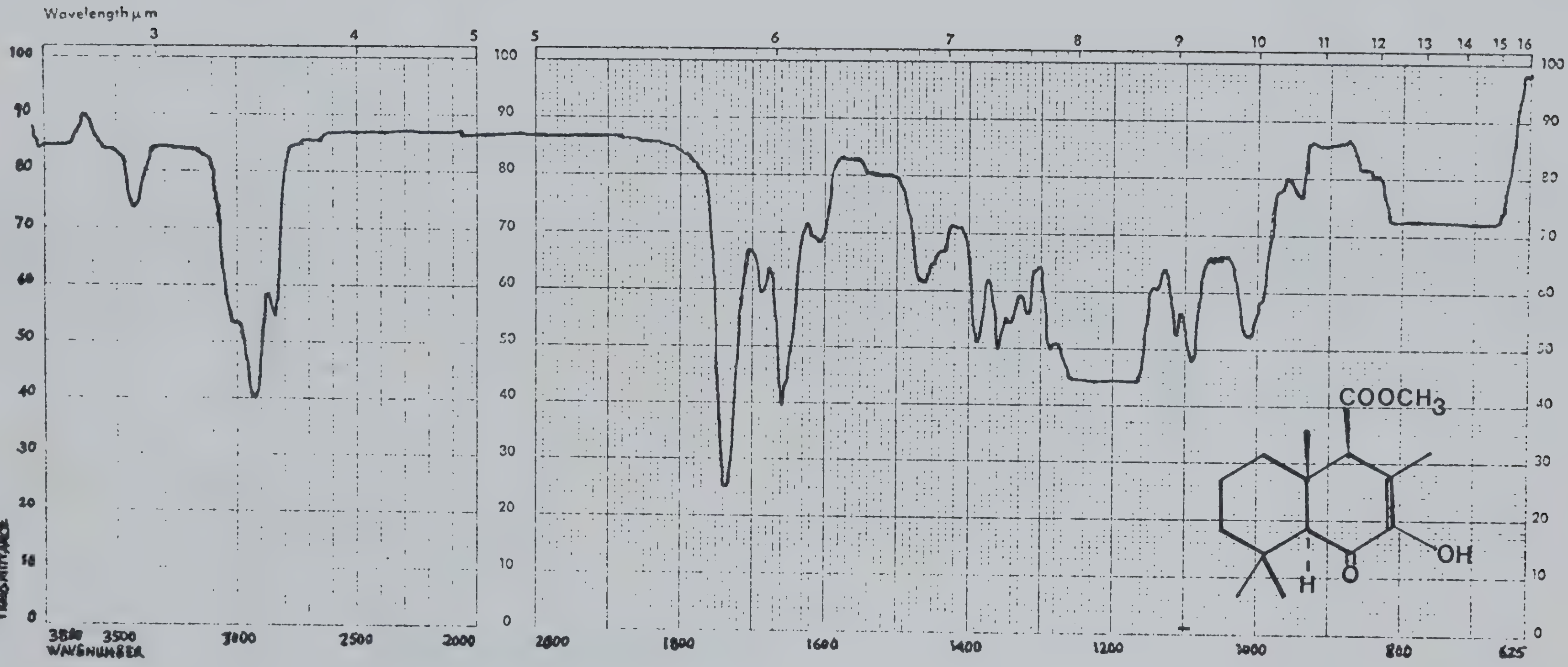


Figure 8. The ir spectrum of 10.

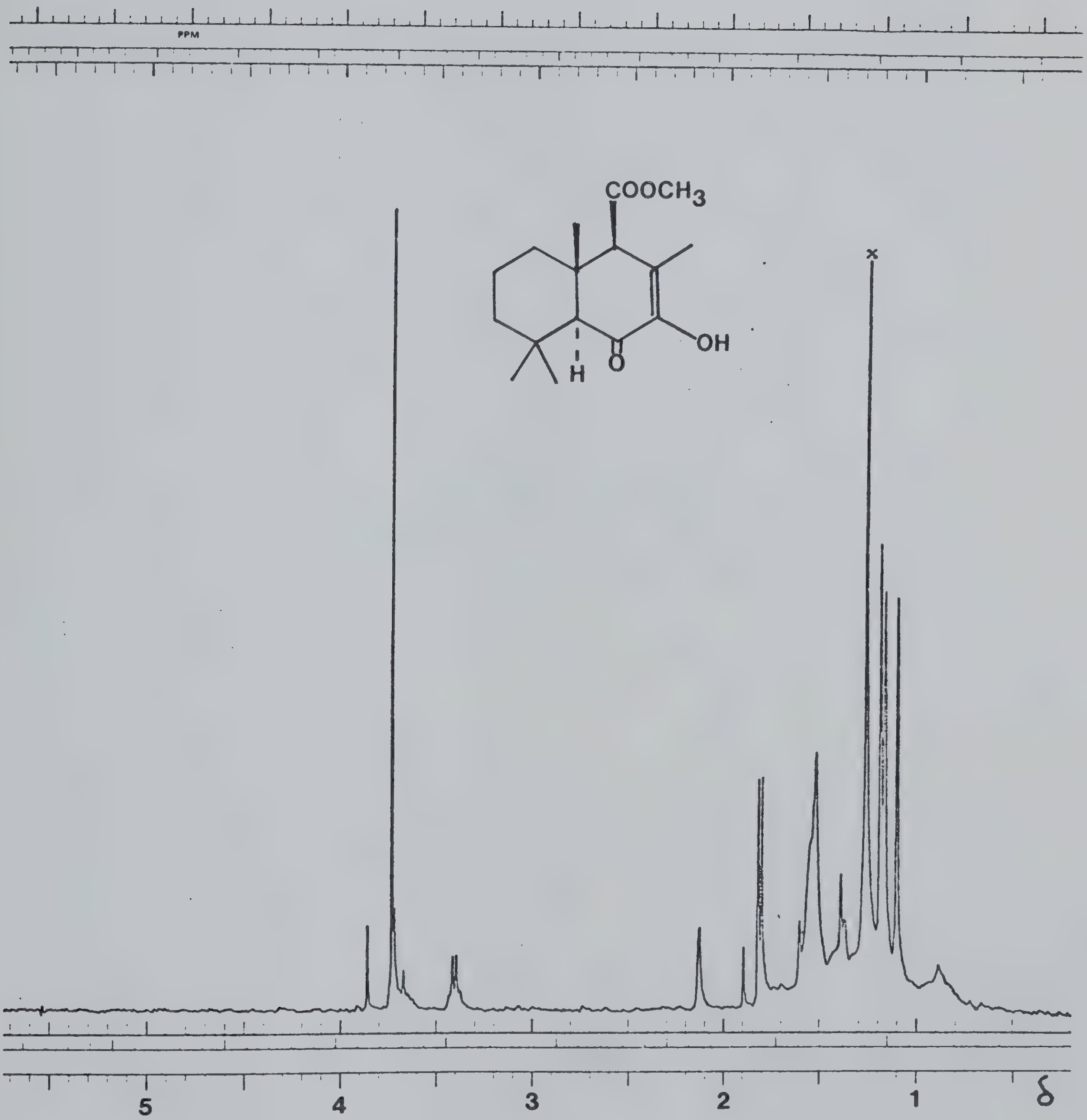
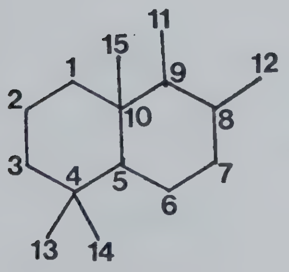


Figure 9. The ^{1}Hmr spectrum of 10.

II: A SYNTHETIC APPROACH TO BICYCLOFARNESANE SESQUITERPENES

INTRODUCTION

The bicyclofarnesane class of sesquiterpenes (1) has been known since the 1950's when Djerassi and coworkers elucidated the structure of iresin (2).[1] Since then bicyclofarnesanes have been isolated from a variety of sources including trees and shrubs, tobacco, liverwort, water pepper, and Penicillum species.[2] Recently, Kubo and colleagues[3] reported the isolation and characterization of potent army worm antifeedants such as warburganal (3) which contain the bicyclofarnesane skeleton. These antifeedants, isolated from the East African Warburgia plants cause starvation of widely occurring African crop pests. It is conceivable that these potent antifeedants may provide another method for controlling pest insects in the field or during crop storage. Our



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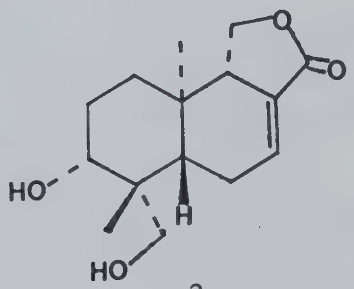

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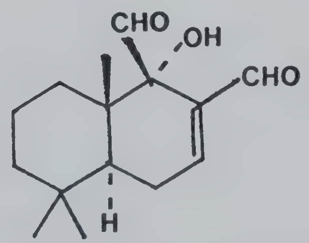

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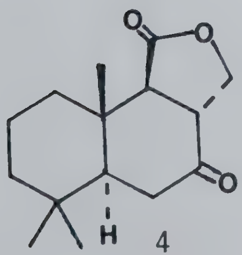

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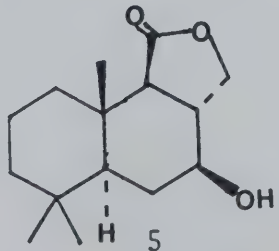

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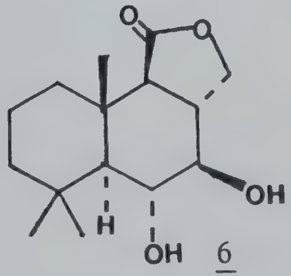
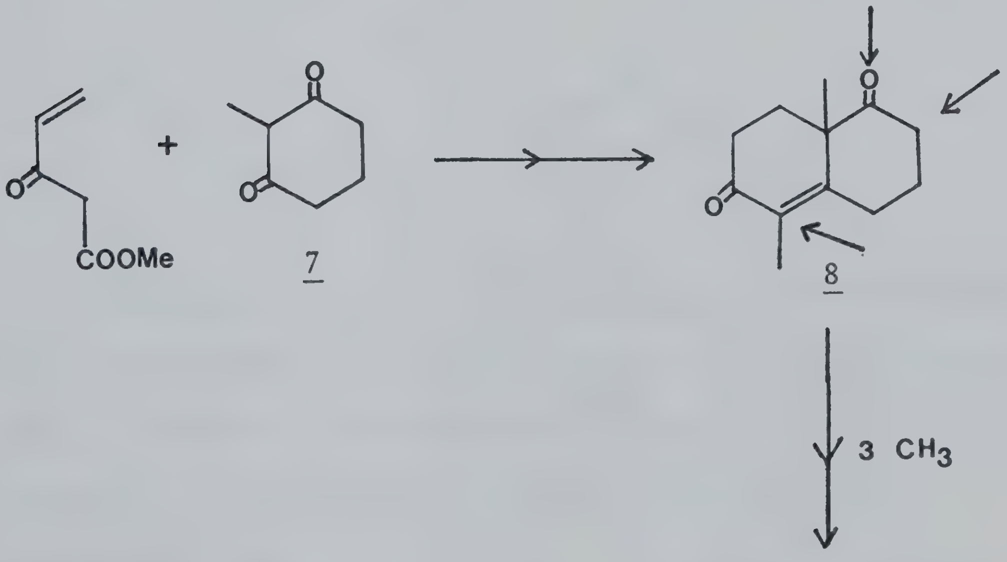


6

studies of the metabolites of *Mycocalia reticulata* also produced interesting bicyclofarnesane (drimane) type sesquiterpenes 4, 5, and 6.[2] We therefore undertook the design of an efficient synthesis to compounds 3, 4, 5, and 6.

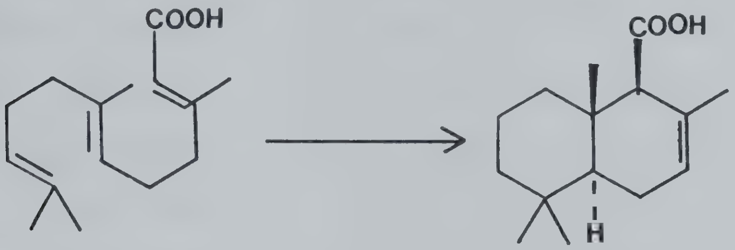
In any synthetic design of these bicyclofarnesanes, one must incorporate a minimum of three chiral centers together with a *gem*-dimethyl group and an angular methyl group in the target molecules.

Basically, there are four known synthetic approaches to the bicyclofarnesane skeleton. One approach involves Robinson annelation of diketone 7 to form the functionalized bicyclo[4.4.0] system 8[4] as shown. Subsequent introduction of the three remaining carbons would complete the sesquiterpene skeleton.



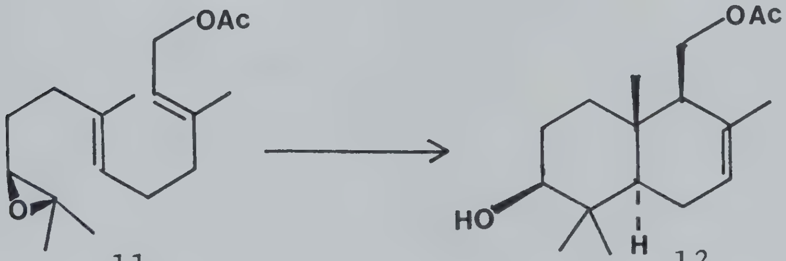
a bicyclofarnesane

Secondly, cyclization of farnesyl derivatives provides a biomimetic entry into the bicyclofarnesane system. This approach first introduced by Caliezi and Schinz[5] in 1949, involves for example, treatment of farnesyl 9 with boron trifluoride to give bicyclofarnesane 10 in 35% yield.[6] E.E. van Tamelen and co-workers[7] similarly



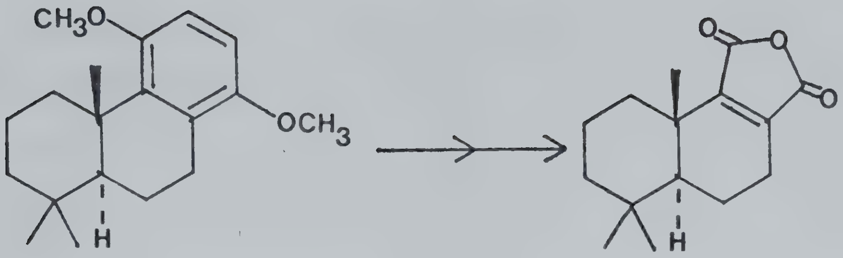
9 10

cyclized farnesyl epoxide 11 in modest yield to give alcohol 12.



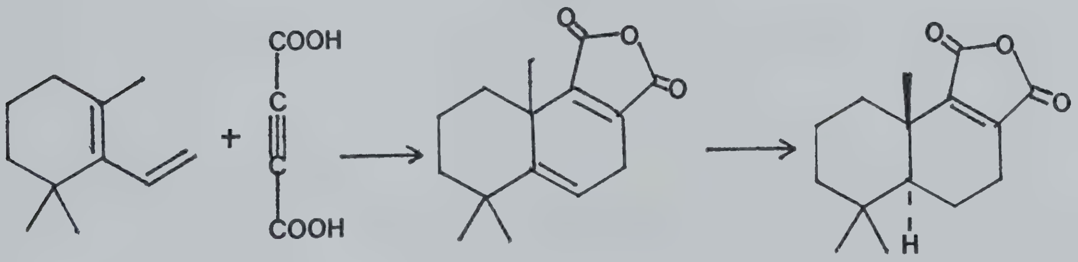
11 12

Degradation of the structurally similar diterpenoid resin acids provides another route to the bicyclofarnesanes. Recently, Pelletier and Ohtsuka[8] converted podocarpic derivative 13 into the sesquiterpene (+)-winterin (14).



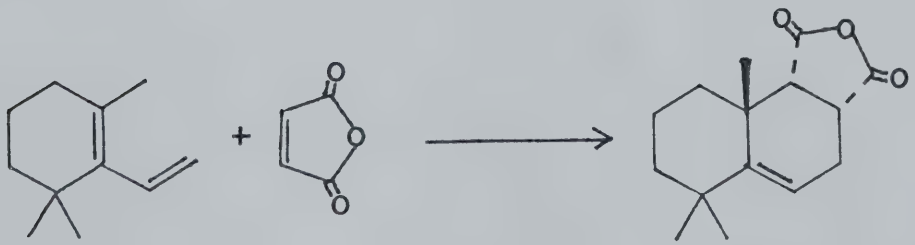
13 14

Finally, a Diels-Alder approach would appear to be an obvious synthetic alternative to the bicyclo[4.4.0] system. However, there are only two reported cases of a direct Diels-Alder route to bicyclofarnesane sesquiterpenes. Both use diene 15. Reaction of diene 15 with acetylenedicarboxylic acid gives adduct 16 in only 4% yield which is then hydrogenated to (±)-winterin (14).[9]



15 16 14

Diene 15 has also been reported to react with maleic anhydride to give adduct 17 in low yield.[10] The low yields



15 17

reported suggest that the incorporation of an angular methyl group is not a facile process in the Diels-Alder reaction. The presence of the *gem*-dimethyl group may also cause additional steric interference to the Diels-Alder reaction.

Our synthetic approach utilizes a similar Diels-Alder reaction, incorporating all the necessary carbon framework in one key step. We sought to improve the previous Diels-Alder reactions by using a more reactive diene 18a to give functionalized adducts 19 and 21 as shown in Figure 1. A Diels-Alder reaction of diene 18a with maleic anhydride is expected to yield adduct 19 which can lead to the metabolites 4, 5, and 6. Compound 19 can be reduced[11] and subsequently epimerized[12] to lactone 20. Further functional group manipulation can produce the drimanic lactones 4, 5, and 6.

On the other hand, the dimethyl acetylenedicarboxylate adduct 21 can be expected to provide a basis for elaboration into warburganal (3). The sensitive aldehyde function is preferentially unmasked at the end of the synthesis after the key Wharton reaction. Hydrogenation[9] of adduct 21 is expected to give the *trans*-fused structure 22 which upon hydride reduction and protection of the primary alcohols should yield acetonide 23. Oxidations of 23 should produce epoxy ketone 24 which could be

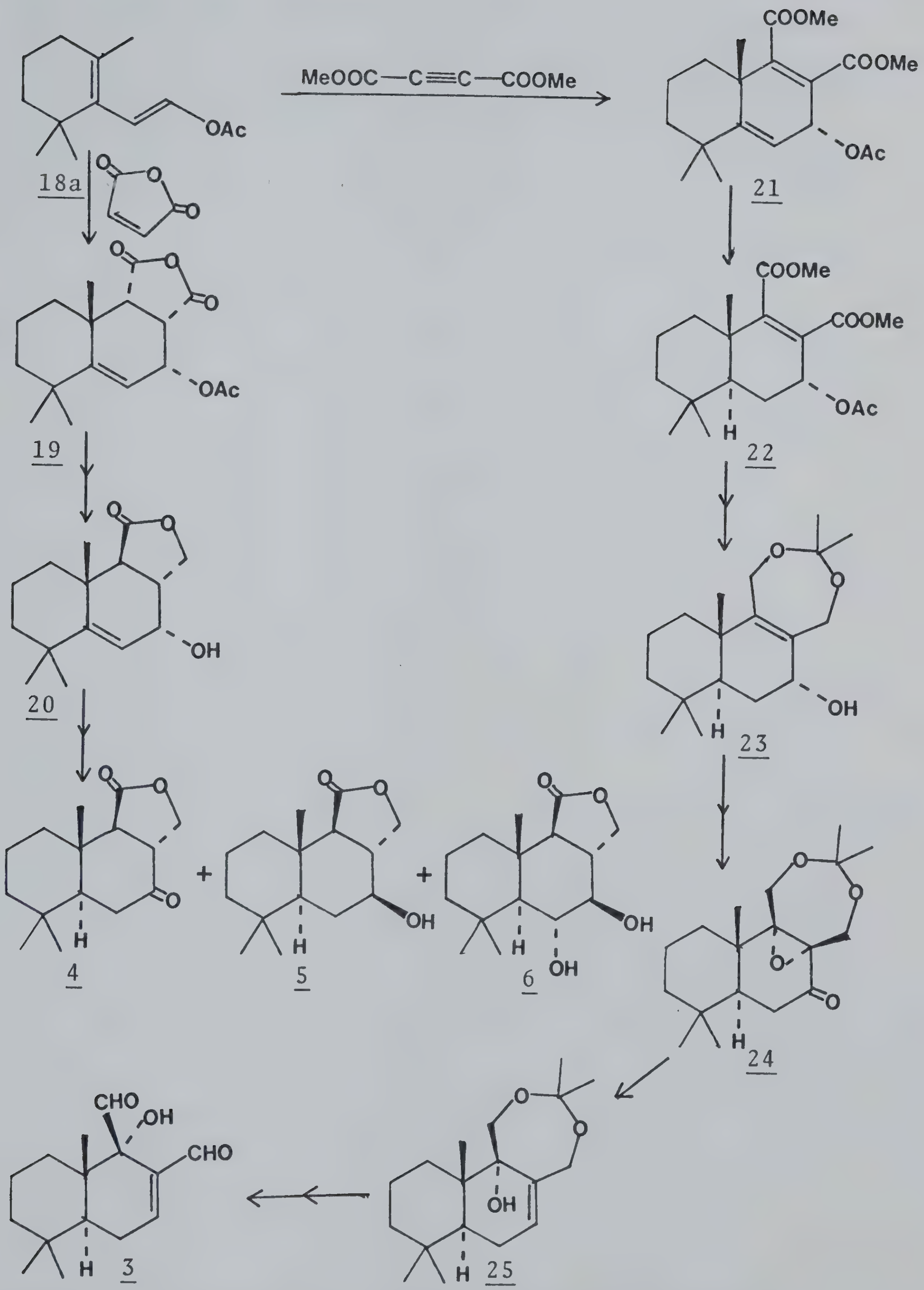
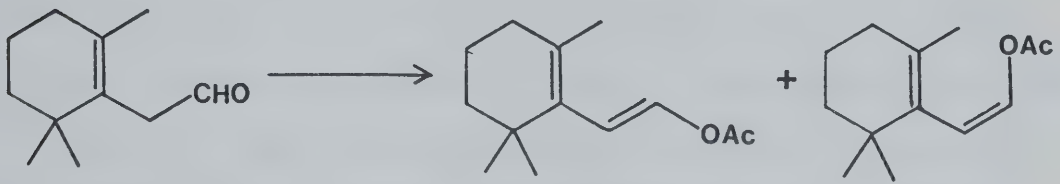

MeOOC—C≡C—COOMe
OAc
18a
19
20
4
5
6
21
22
23
24
25
3
COOMe
OH
H
CHO

Figure 1. The synthetic plan to bicyclofarnesanes.

subjected to the conditions of the Wharton reaction to give the allylic alcohol 25. Deprotection and oxidation of the primary alcohols would then yield the desired warburganal (3).

DISCUSSION AND RESULTS

The starting material for the synthesis is β-homocyclocitral (26)[*]. The enol acetate 18 was formed by treating β-homocyclocitral with a catalytic amount of p-toluenesulfonic acid in refluxing isopropenyl acetate.



26 18a 18b

The distilled product was obtained in 67% yield as a 35:65 mixture of E- and Z-enol acetates, 18a and 18b respectively. This mixture was used for the subsequent Diels-Alder reactions with both maleic anhydride and dimethyl acetylenedicarboxylate.

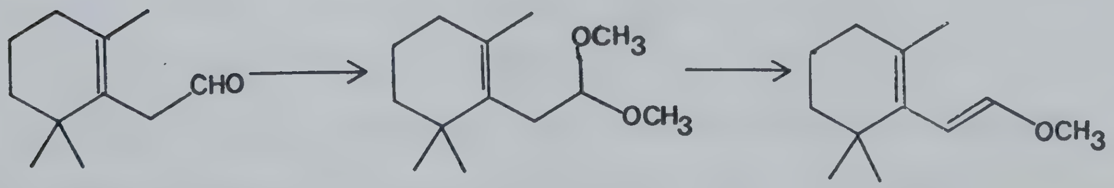
Enol acetates 18a, b were treated with maleic anhydride under various conditions. Refluxing DME, xylene, diglyme, and benzene/$AlCl_3$ in the Diels-Alder reaction all resulted in only starting materials. Formation of the enol acetates in the presence of maleic anhydride gave only the enol acetates 18a, b and maleic anhydride. None of the desired adduct was detected.

[*] β-Homocyclocitral was kindly provided by Dr. W.I. Taylor of International Flavors and Fragrances, Union Beach, New Jersey.

Addition of the dienophile dimethyl acetylenedicarboxylate also proved unsuccessful, giving no Diels-Alder adduct. Only starting materials were recovered. The conditions used for the attempted reaction of enol acetates 18a, b with dimethyl acetylenedicarboxylate were benzene/room temp., benzene/reflux, toluene/reflux, ether/$BF_3 \cdot OEt_2$/0°, ether/$BF_3 \cdot OEt_2$/room temp., diglyme/reflux, benzene/$AlCl_3$/reflux, and xylene/sealed tube/150°.

Similar conditions to those reported for diene 15[9] were also investigated. Enol acetates 18a, b and acetylenedicarboxylic acid were heated in diglyme at 110°, but only starting materials were obtained.

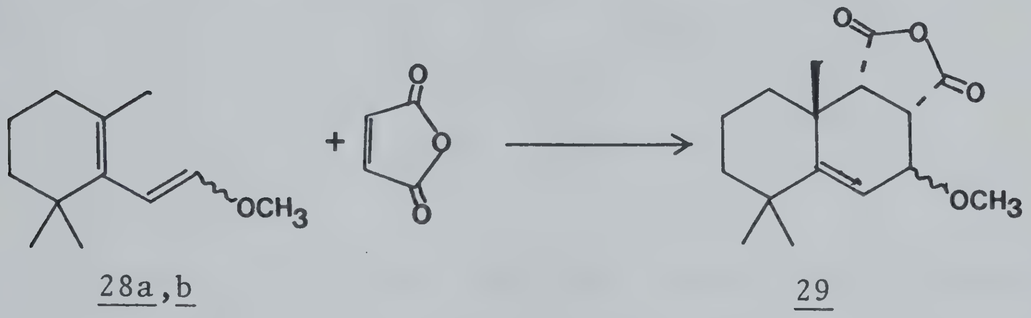
Apparently a more reactive diene is required for the Diels-Alder reaction. The methyl enol ether of β-homocyclocitral was chosen. The enol ether 28a could not be formed directly from β-homocyclocitral (26) with methanolic hydrogen chloride. No reaction was observed. However, the dimethylacetal 27 was formed quantitatively from 26 using 1.5 equivalents of trimethylorthoformate and ammonium chloride in refluxing methanol.



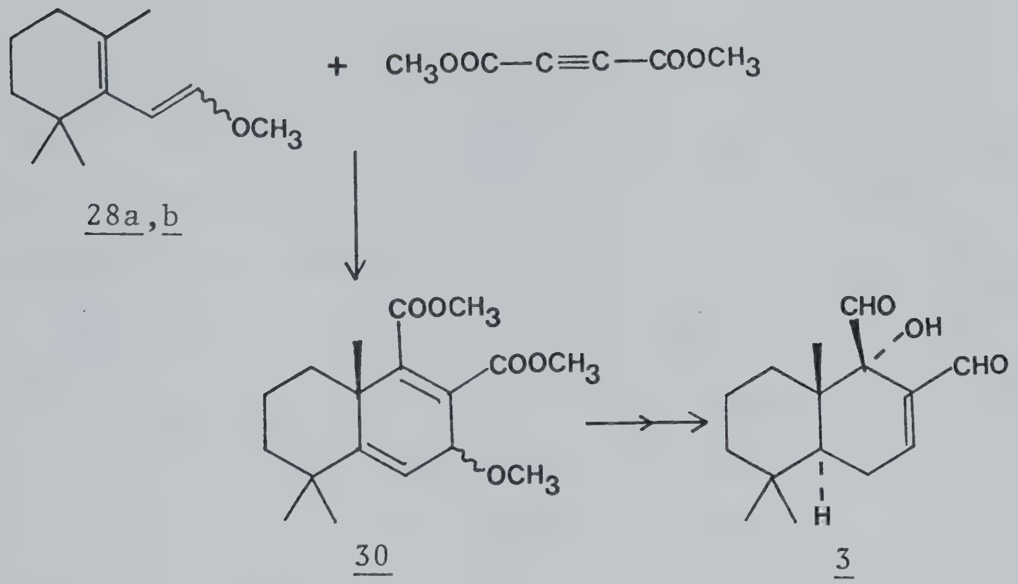
26 27 28a

Removal of methanol from acetal *27* to give enol ether *28a* was somewhat of a problem. Pyrolysis at 120-130° was unsuccessful. Treatment of *27* with phosphoric acid/70°, benzene/reflux, benzene/alumina/reflux, and *n*-BuLi/ether gave only starting material. Finally, phosphorus pentoxide in refluxing benzene was found to eliminate methanol from *27* to give an 87% yield of distilled enol ether. The *E*- and *Z*-enol ethers, *28a* and *28b* respectively were obtained in a 65:35 ratio from this reaction. It was expected that the *E*-enol ether *28a* would react faster than the *Z*-enol ether *28b* in a Diels-Alder reaction, since an s-cisoid orientation would be more favorable in *28a*. Therefore attempts were made to increase the *E* to *Z* ratio of *28*. Lower temperatures (-78° to room temp.) in the phosphorus pentoxide/benzene reaction with *27* gave the same ratio of *28a* and *28b*. Treatment of the acetal *27* with phosphorus oxychloride/pyridine gave after aqueous workup β-homocyclocitral (*26*). Heating acetal *27* with a small amount of diisopropylethylammonium-*p*-toluenesulfonate at 130° while distilling off methanol[13] did not improve the *E* to *Z* ratio of enol ethers *28a*, *b*. Since we were unsuccessful in obtaining improved *E* to *Z* ratios, the enol ether mixture (*E* to *Z*, 65:35) obtained from the phosphorus pentoxide/refluxing benzene method was used in subsequent Diels-Alder reactions.

Dienes 28a, b were first treated with maleic anhydride in attempts to obtain the Diels-Alder adduct 29. Heating an approximately equimolar mixture of dienes 28a, b and maleic anhydride in refluxing toluene and in refluxing xylene gave mostly starting materials. Sealed tube reactions were performed in benzene/250°, benzene/180°, and xylene/140°; all giving none of the desired adduct 29, but predominantly starting materials. Using similar conditions to that reported for diene 15 and maleic anhydride,[10] dienes 28a, b and maleic anhydride in chloroform were heated in a sealed tube at 95°. The only identifiable substances from this reaction were starting materials and β-homocyclocitral (26). Thus we could not obtain the key Diels-Alder intermediate 29 for the projected syntheses of the drimanic lactones 4, 5, and 6.



Reaction of dienes 28a, b with dimethyl acetylenedicarboxylate could provide the Diels-Alder adduct 30 which may be suitable for conversion into warburganal (3).



28a,b

30

3

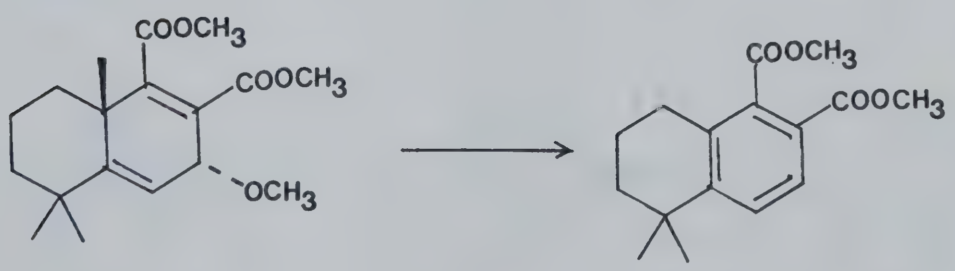
A variety of conditions were tested for the Diels-Alder reaction of dienes 28a, b with dimethyl acetylenedicarboxylate (~1.3 equivalents). Using refluxing benzene as the solvent, the Diels-Alder reaction resulted in only starting material. However increasing the temperature of the Diels-Alder reaction to that of refluxing xylene provided a small amount of the 7-α-methoxy adduct 30a. Using more drastic conditions, sealed tube reactions were carried out in benzene at 250°, 180°, and 150°. The only identifiable material obtained was the Z-diene 28b. A sealed tube reaction in chloroform at 95° gave starting materials. Employing the solvent xylene which had been partially successful, a sealed tube reaction was carried out at 150°. A 15-20% yield of the Diels-Alder adducts 30a, b was obtained after 3.5 days.

The Diels-Alder reaction in toluene at 150°/3 days gave no adduct, but the Z-diene 28b as the only identifiable product. Sealed tube reactions in xylene at varying temperatures were then investigated. At 180°/1 day only diene 28b was identified. At 130°/7 days a ~25% yield of adducts 30a, b was obtained. Lower temperatures (120°) for 16 days resulted in an unimproved yield of the adduct. Surprisingly, reaction in refluxing xylene for 7 days yielded only a small amount of the adduct. We have no explanation for the variable yields of the adduct in different solvents.

The optimum conditions devised (xylene/sealed tube/ 130°/7days) for 28a, b and dimethyl acetylenedicarboxylate gave a 45% yield of the adducts 30a, b isolated by column chromatography. The adducts exhibited the proper ir, ^{1}Hmr, and mass spectral data. According to the ^{1}Hmr spectrum, an approximately equimolar mixture of the 7α- and 7β-methoxy adducts 30a and 30b respectively, was obtained. Adduct 30a, formed from the E-diene 28a, exhibited in the ^{1}Hmr spectrum a smaller coupling constant (2.5 Hz) between the C-6 and C-7 hydrogens than adduct 30b (5.5 Hz) formed from the Z-diene 28b. The dihedral angle between the hydrogens at C-6 and C-7, obtained by examination of Dreiding models is about 85° for compound 30a and about 40° for compound 30b.

Also isolated from the crude Diels-Alder reaction mixture was the unreacted *Z*-diene **28b**, accounting for all the *Z*-diene used. It appears that the dimethyl acetylenedicarboxylate polymerizes before the slow reacting **28b** can be completely consumed. In an attempt to drive the Diels-Alder reaction towards completion, 2.3 equivalents of dimethyl acetylenedicarboxylate were used, but this did not improve the yield.

A compound with the molecular formula $C_{16}H_{24}O_4$ (high resolution ms) was another major reaction product from the Diels-Alder reaction. The aromatic (ir, uv, ^{1}Hmr) compound contained two methyl esters as evidenced by the ir absorption at 1730 cm^{-1} and the methyl singlets at δ3.91 and 3.83 in the ^{1}Hmr spectrum. The ^{1}Hmr spectrum also shows two *ortho* coupled (8 Hz) aromatic hydrogens as doublets at δ7.82 and 7.44 and a two methyl singlet at δ1.28. Structure **31** is proposed for this compound.



30a

31

Compound *31* is probably formed from adduct *30a* by loss of C_2H_6O. It is unlikely to arise from the β-methoxy adduct *30b* since all the *Z*-diene *28b* is accounted for as either adduct *30b* or unreacted *28b*. Formation of compound *31* may be acid catalyzed. However, addition of triethylamine or sodium carbonate to the Diels-Alder reaction did not retard the formation of the aromatic compound *31*. Since aromatization to *31* could be a free-radical process, the radical inhibitor 2,6-di-*t*-butyl-4-methylphenol was included in the reaction mixture but the production of *31* remained unchanged.

With a bicyclofarnesane adduct now available in much improved yields, we tested a more direct route to the Wharton precursor *34* as outlined in Figure 2.

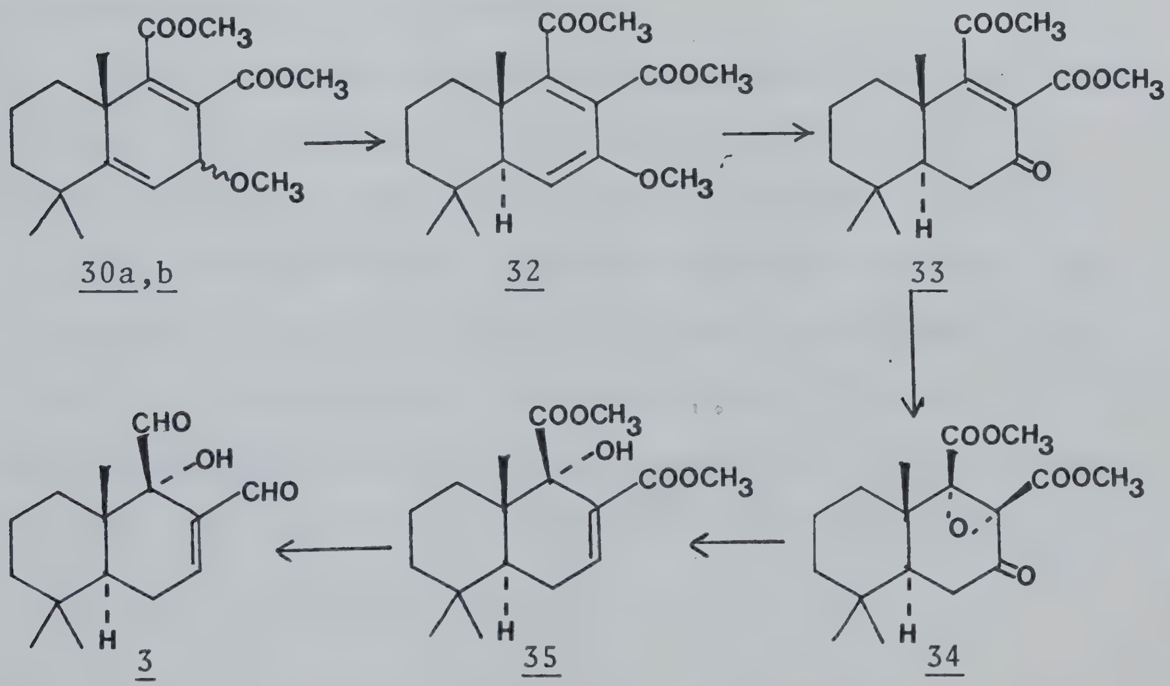

COOCH3
COOCH3
OCH3
30a,b
COOCH3
COOCH3
OCH3
H
32
COOCH3
COOCH3
O
H
33
COOCH3
COOCH3
O
O
H
34
COOCH3
OH
COOCH3
H
35
CHO
OH
CHO
H
3

Figure 2. The Wharton approach to warburganal.

Several attempts were made to convert 30a, b directly into ketone 33 with aqueous hydrochloric acid in THF at 0°, room temperature, and reflux. However, mainly starting material was recovered. Treatment of 30a, b with methanolic sodium methoxide failed to yield enol ether 32, no reaction being observed.

With this failure, we returned to the synthetic scheme outlined earlier in Figure 1, the acetyl group now replaced by a methyl group. Hydrogenation of adducts 30a, b with platinum oxide/ether/room temp. at one atmosphere gave unexpectedly the hydrogenolized product 36 (Figure 3). The biallylic methoxy group appears to be quite labile. Hydrogenation of 30a, b with 5% Pd-C/ether/room temp. at one atmosphere with a small amount of triethylamine gave no reaction.

Since we anticipated possible problems in effecting methyl ether cleavage in the conversion to alcohol 23, we abandoned the synthetic strategy in Figure 1 and concentrated our efforts on a new approach via alkene 36 as shown in Figure 3. Stereoselective epoxidation of 36 from the less hindered α-face would give 37, which upon base promoted rearrangement could yield the allylic alcohol 38. Subsequent reduction of the ester groups would produce warburganal (3).

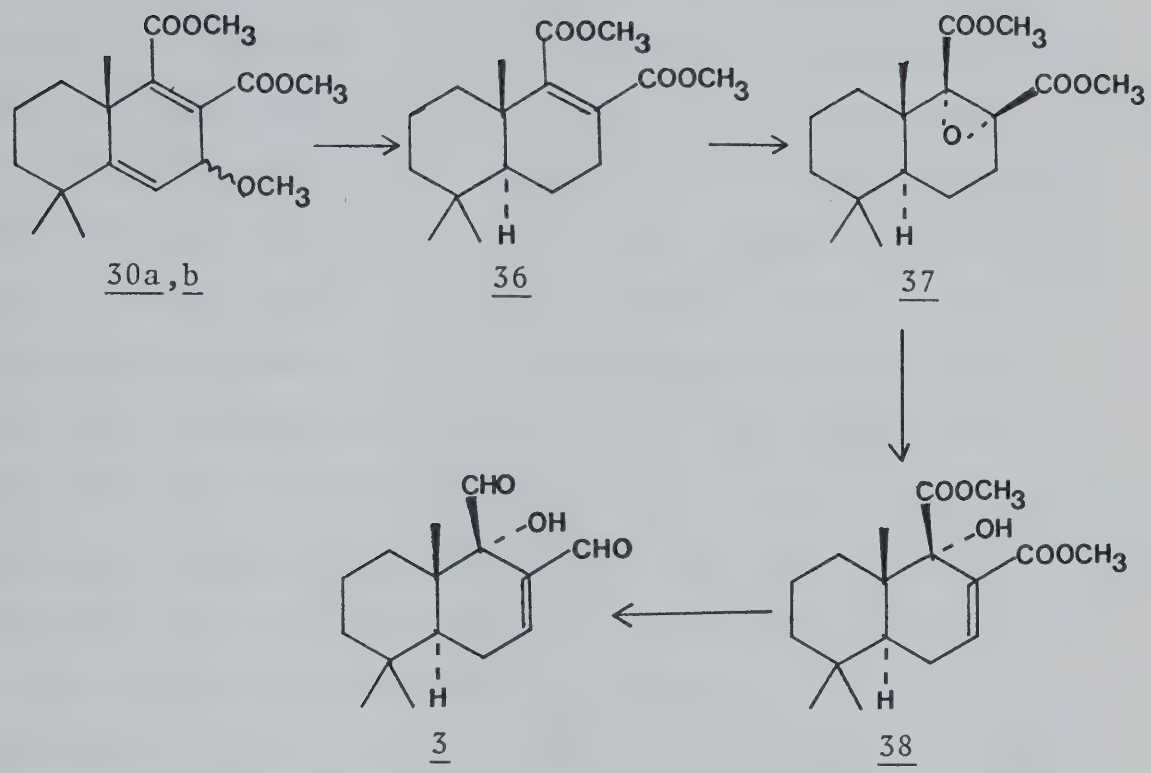

COOCH3
COOCH3
OCH3
30a,b
COOCH3
COOCH3
H
36
COOCH3
COOCH3
O
H
37
COOCH3
OH
COOCH3
H
38
CHO
OH
CHO
H
3

Figure 3. A synthetic approach to warburganal via diester epoxide 37.

Conversion of 30a, b to alkene 36 can be effected under various conditions at one atmosphere and room temperature: 10% Pd-C/HOAc, PtO$_2$/ether, 10% Pd-C/ether, and 10% Pd-C/CH$_3$OH; the last method being the most reproducible in about 50% yield.

Epoxidation of alkene 36 to epoxide 37 proved to be very difficult. Numerous methods were investigated.

Alkaline hydrogen peroxide in methanol did not react with *36*. Treatment of alkene *36* with *m*-chloroperbenzoic acid at room temperature or in refluxing chloroform, 1,2-dichloroethane, or toluene all failed to produce any epoxide *37*. Addition of the radical inhibitor 2,6-di-*t*-butyl-4-methylphenol to prevent thermal decomposition of *m*-chloroperbenzoic acid[14] in refluxing chloroform and 1,2-dichloroethane did not epoxidize *36*. Aqueous sodium hypochlorite in dioxane[15] or pyridine[16] gave no reaction with *36*. Epoxidation with *t*-butyl hydroperoxide/triton B in THF[17] was also unsuccessful. The powerful oxidant peroxytrifluoroacetic acid[18] was reacted with *36* in methylene chloride buffered with sodium phosphate. The starting material was consumed overnight. Chemical ionization mass spectrometry showed the addition of one oxygen atom as in the desired epoxide *37*. However, treatment of this material with lithium diisopropylamide[19] failed to produce the desired alcohol *38*.

Since epoxidation of diester *36* proved so difficult, we decided to investigate the epoxidation of diol *39* which should be more amenable to epoxidation. (See synthetic outline in Figure 4.) Diol *39* was obtained by hydrogenation of *30a*, *b* over PtO_2 in ether, removal of the catalyst by filtration, and treatment of the resulting ethereal solution with lithium aluminum hydride.

Chromatography of the reaction products yielded diol 39 in low yield (22%) together with isomer 40 (10-15%) and the over reduced diols 41 (35%).

In the production of diols 41, it was not known whether the reduction of the C-8 double bond occurred during the hydrogenation or the hydride reduction step. Compound 36 was presumed to have isomerized to diol 40 during the hydride reduction. It was felt that use of a different hydride reagent might solve both these problems. Hydrogenation of 30a, b followed by treatment with diisobutylaluminum hydride to prevent possible 1,4-reduction,[20] gave an unimproved yield of the desired diol 39, along with the byproducts 40 and 41. Therefore the over reduced product 41 must arise during the hydrogenation. A shorter reaction time in the hydrogenation step could probably eliminate this problem.

The ^{1}Hmr spectrum of 40 appeared to be overly complicated for a single compound. It was possible that we were dealing with C-9 epimers. The ^{13}Cmr spectra of both derivatives 42 and 43 confirmed the existence of two isomers. The ^{1}Hmr spectra of the derivatives also supported the C-9 epimeric structures 42 and 43. Separation of the diacetyl derivatives 43 could not be achieved by chromatography, including chromatography over silver nitrate impregnated silica. Gas chromatography

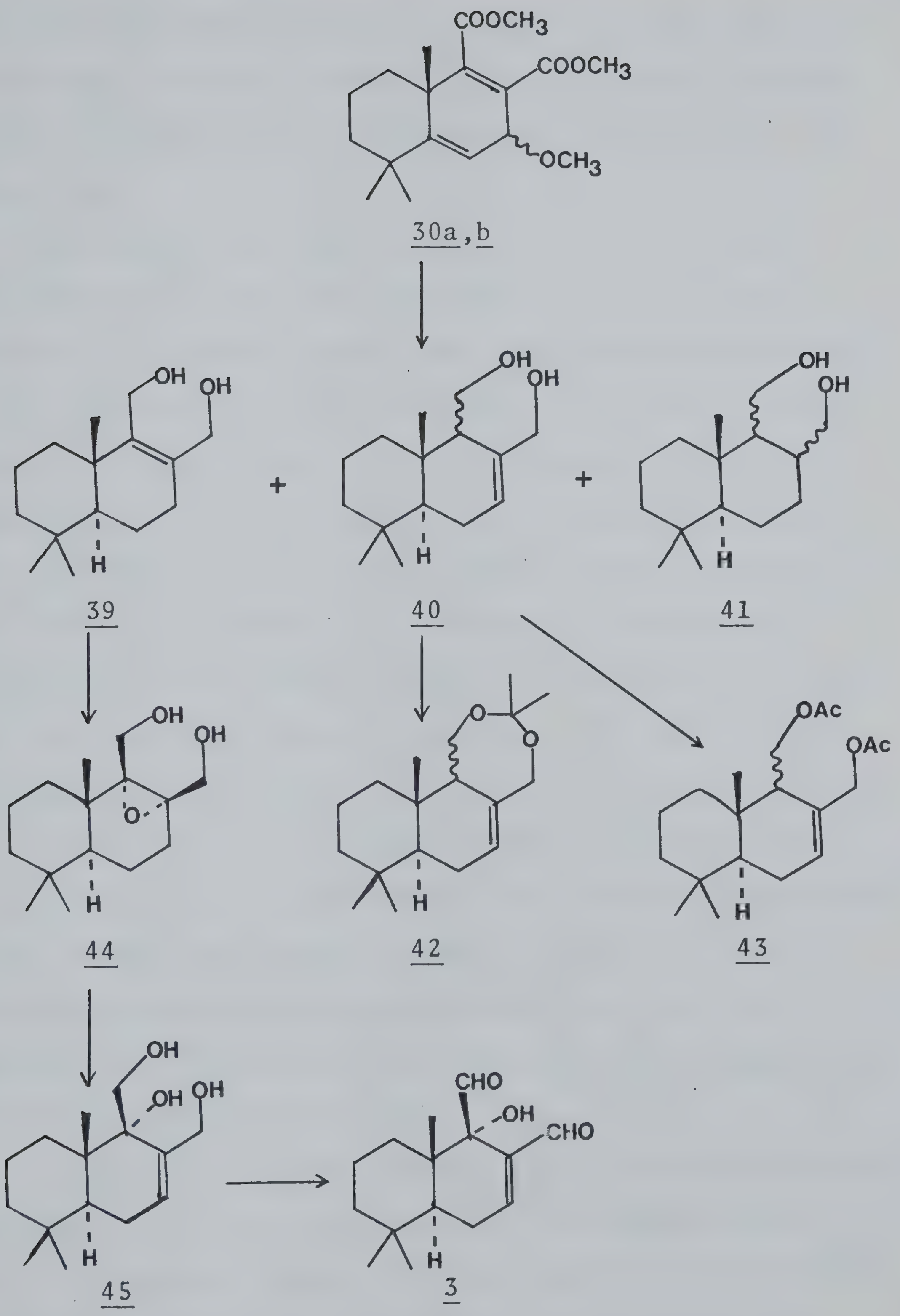

COOCH3
COOCH3
OCH3
30a,b
OH
OH
H
39
+
OH
OH
H
40
+
OH
OH
H
41
OH
OH
O
H
44
O
O
H
42
OAc
OAc
H
43
OH
OH
OH
H
45
CHO
OH
CHO
H
3

Figure 4. A synthetic approach to warburganal via diol epoxide 44.

(Carbowax 20M, OV-225) failed to separate the acetonide epimers 42. Moreover isomers 43 could not be isomerized to the Δ^8-compound with *p*-toluenesulfonic acid in chloroform.

Stereoselective epoxidation of 39 with *m*-chloroperbenzoic acid gave the α-epoxide 44 in high yield. Presumably oxidation occurs from the less-hindered α-face of 39. Base promoted rearrangement of epoxide 44 to the allylic alcohol 45 was next investigated. Treatment of 44 with *n*-Buli in ether gave mostly starting material. The solubility of the dioxygen dianion generated from 44 was probably a problem. In attempts to improve the solubility of the dianion of 44, DMF and HMPA/ether were used as solvents. However, treatment of 44 with *n*-Buli in these solvents resulted in recovered starting material.

Protection of the hydroxyl groups appeared to be a likely solution to the problem. We therefore decided to follow a modified scheme as shown in Figure 5. The alcohols would be protected as acetonide 47 and the epoxide would then be rearranged to 48 before deprotection to give the desired triol 45.

Acetonide 46 formed readily from 39 in 2,2-dimethoxypropane with a catalytic amount of *p*-toluenesulfonic acid. Epoxidation with *m*-chloroperbenzoic acid proceeded smoothly to give what is presumably the α-epoxide 47.

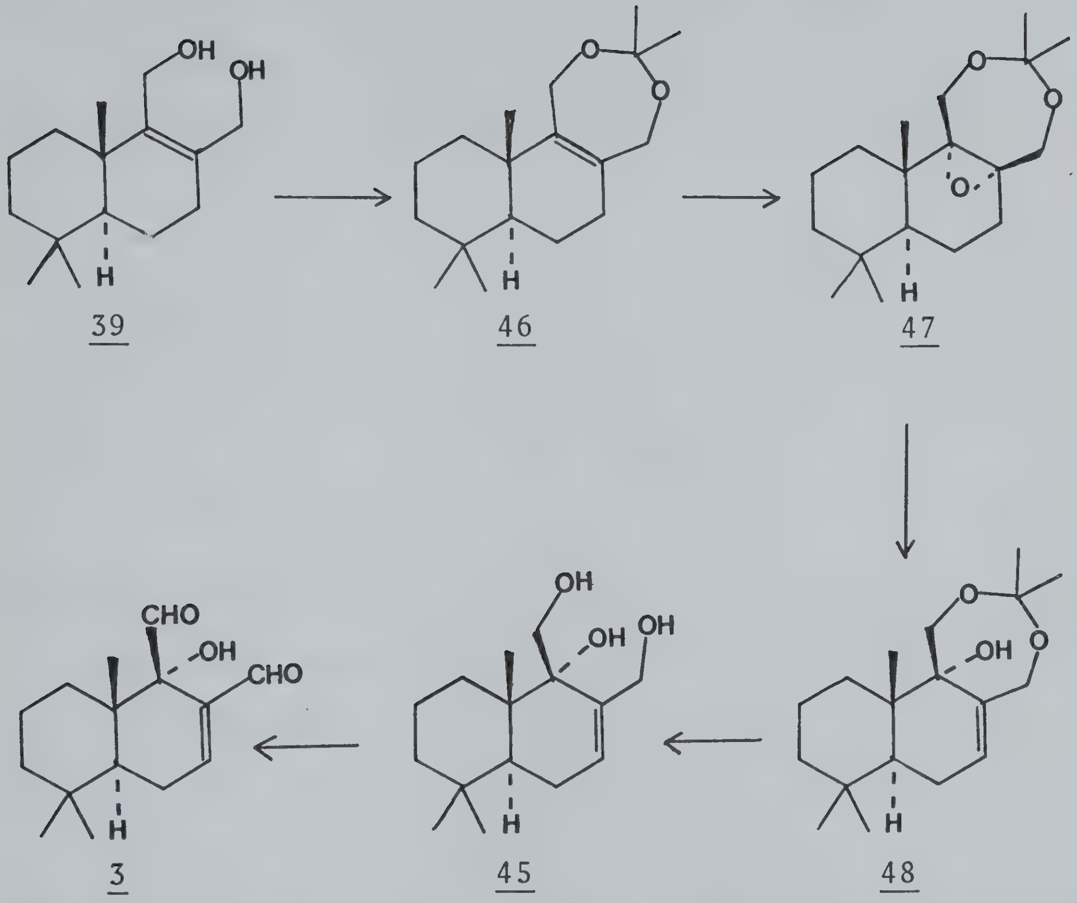
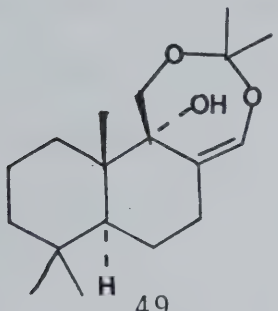


Figure 5. A synthetic approach to warburganal via acetonide epoxide 47.

Attempts were then made to convert epoxide 47 into allylic alcohol 48 with base. Treatment of 47 with *n*-BuLi gave promising results. The products absorbed in the hydroxyl and carbon-carbon double bond regions of the ir spectrum. The ^{1}Hmr spectrum of the crude products showed a singlet at δ6.0 and a broad doublet of doublets at δ5.8 in about equal proportion. The δ5.8 signal could be assigned to the desired compound 48 on the basis of the

multiplicity observed. The δ6.0 signal, however does not allow differentiation between structures 49 and 50 on the basis of ^{1}Hmr spectrum. Although isomer 49 is



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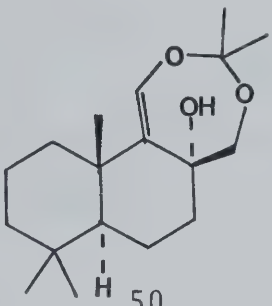
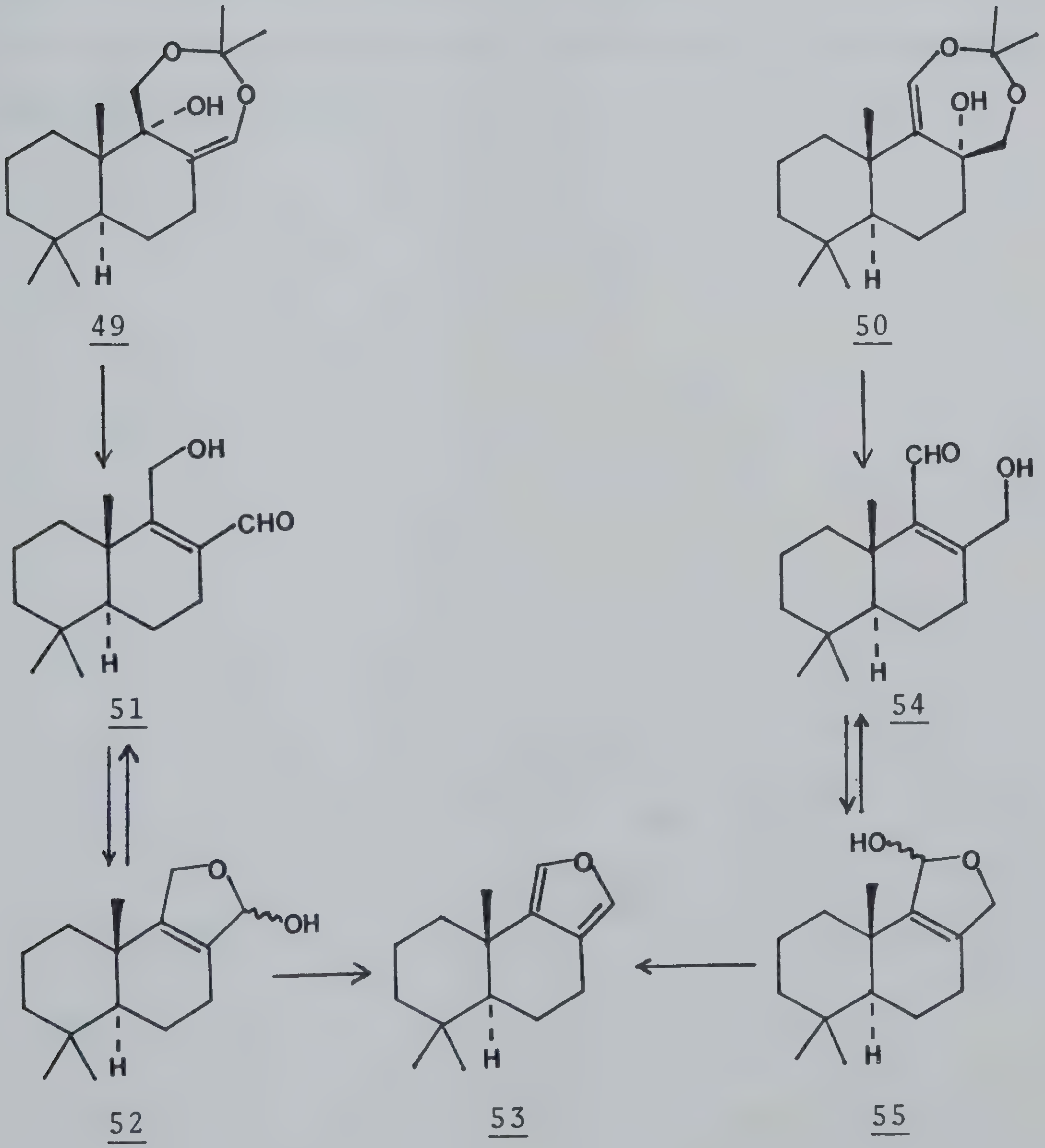


50

probably favored since in 47, the β-hydrogen at C-12 is less hindered to base abstraction than the β-hydrogen at C-11, as indicated by examination of a Dreiding model. One also observes that the β-hydrogen at C-12 may be considerably more sterically shielded than the β-hydrogen at C-7. Thus a bulkier base should give predominantly the desired isomer 48. However, treatment of epoxide 47 with t-BuLi/ether at -78° gave unimproved results. Attempted separation of the compounds by preparative tlc gave only the undesired isomer 49 or 50. When lithium diisopropylamide was used as the base, an isomeric allylic alcohol was obtained as the major product, different from the two obtained previously. Again the ^{1}Hmr spectrum supports either structure 49 or 50.

Additional support of the structures 49 and/or 50 was desirable. Hydrolysis of the acetonides 49 and 50 would be expected to give hydroxy enals 51 and 54 respectively, after dehydration. Hydrolysis of the above lithium diisopropylamide products gave a product showing no carbonyl and no hydroxyl absorption in the infrared. In addition, the ^{1}Hmr spectrum showed a vinyl signal at



49

50

51

54

52

53

55

δ7.1 and high resolution ms indicated a molecular formula of $C_{15}H_{22}O$. On the basis of the spectral data, the furanoid structure 53 is proposed. Furanoid 53 may be formed by dehydration of the hemi-acetal intermediates 52 and 55 under the acidic conditions employed.

Since several of the reactions leading toward the desired product warburganal precede in only very modest yield it appeared that our hope for an efficient synthesis would not be realized and we decided not to pursue this approach any further.

EXPERIMENTAL

Mass spectra were recorded on an A.E.I. MS-50 mass spectrometer coupled to a DS 50 computer, or an A.E.I. MS-9 mass spectrometer (chemical ionization), and are reported as m/e (relative intensity). Unless diagnostically significant only peaks at least 20% as intense as the base peak are reported. Infrared spectra were recorded on a Unicam SP1000 spectrophotometer and uv spectra on a Unicam SP1700 spectrophotometer. Proton magnetic resonance spectra were measured on Varian A-60D, Perkin-Elmer R32, or Varian HA-100 spectrometers with TMS as internal standard. Carbon magnetic resonance spectra were measured on a Bruker HFX-90 spectrometer interfaced to a Nicolet 1085 computer or a Bruker WP-60 spectrometer interfaced to a Nicolet 1080 computer with TMS as internal standard.

Preparative tlc was carried out on 0.75 mm layers of silica gel G (W. Merck, Darmstadt) containing 1% electronic phosphor (General Electric, Cleveland), and materials were detected by uv or by spraying with 30% sulfuric acid and charring. Silica gel (Woelm, < 0.063 mm) was used for column chromatography.

β-Homocyclocitral Enol Acetate, 18a, b

A solution containing β-homocyclocitral (7.0 g), isopropenyl acetate (30 ml), and p-TsOH·H_2O (1.0 g) were

refluxed for 16 h cooled, and water added. The resulting mixture was diluted with ether and the ethereal layer was washed with water (3x), dried ($MgSO_4$), and concentrated under reduced pressure to give a brown liquid (9.1 g). Distillation (92°/3 torr) gave a colorless liquid (5.8 g, 67%) which was a 35:65 mixture of _E_- and _Z_-enol acetates _18a_ and _18b_, respectively.

IR(film): 1755, 1660, 1450(b), 1370, 1220, 935, 730 cm^{-1}.

^{1}HMR($CDCl_3$): δ7.03 (d, J = 7 Hz, _18b_ CH=C_H_-OAc), 6.99 (d, J = 12 Hz, _18a_ CH=C_H_-OAc), 5.84 (bd, J = 12 Hz, _18a_ C_H_=CH-OAc), 5.29 (bd, J = 7 Hz, _18b_ C_H_=CHOAc), 2.10 (s, _18a_ OAc), 2.08 (s, _18b_ OAc), 1.98 (m, allylic), 1.68, 1.52 (s, vinyl CH_3), 0.99 (s, _18a_ CH_3(2)), 0.98 (s, _18b_ CH_3(2)).

MS: m/e calcd. for $C_{13}H_{20}O_2$: 208.1464, found: 208.1470(27), 166(100), 151(86), 107(23).

β-Homocyclocitral Dimethylacetal, 27

A mixture of β-homocyclocitral (6.6 g, 40 mmole), trimethylorthoformate (6.4 ml, 60 mmole), and ammonium chloride (100 mg) in anhydrous methanol (12 ml) was refluxed for 2 h and then diluted with ether. The ethereal solution was washed with saturated $NaHCO_3$ solution, water; dried ($MgSO_4$); and concentrated under reduced pressure to

give β-homocyclocitral dimethylacetal 27 quantitatively. A small amount was distilled (116°/12 torr) through a short Vigreaux column for analysis.

IR(film): 1470(b), 1360, 1120, 1080, 1055 cm^{-1}.

^{1}HMR($CDCl_3$): δ6.42 (t, 1, J = 5 Hz, $C\underline{H}(OCH_3)_2$), 3.36 (s, 6, OCH_3), 2.40 (bd, 2, J = 5 Hz, $C\underline{H}_2$-$CH(OCH_3)_2$, 1.9 (m, 2, allylic), 1.67 (bs, 3, vinyl CH_3), 1.01 (s, 6, CH_3).

Chemical Ionization (NH_3) MS: m/e 442(8) 2M + 18, 410(8), 378(57), 247(13) M + 35, 230(12) M + 18, 198(7), 183(100), 166(65), 151(7), 75(48), 52(48).

ANALYSIS: calcd. for $C_{13}H_{24}O_2$: C 73.54, H 11.39; found: C 73.37, H 11.37.

β-Homocyclocitral Enol Ether, 28a, b

The dimethylacetal 27 was dissolved in anhydrous benzene (20 ml) and phosphorus pentoxide (4 g) was added. The mixture was refluxed for 1 h, and additional phosphorus pentoxide (2 g) was added and reflux continued for 1 h. The reaction mixture was allowed to cool and the benzene layer was decanted off. The dark brown residue was washed well with ether and the washings combined with the benzene layer. The combined organic layers were then concentrated under reduced pressure and distilled (98°/12 torr) to give a colorless liquid (6.2 g, 87%) which was a 65:35 mixture of E- and Z-enol ethers, 28a

and 28b respectively.

IR(film): 1655, 1640, 1465(b), 1215, 1095, 940, 735 cm^{-1}.

^{1}HMR($CDCl_3$): δ6.19 (d, J = 13 Hz, 28a CH=CH-OCH_3), 5.90 (d, J = 7 Hz, 28b CH=CH-OCH_3), 5.17 (bd, J = 13 Hz, 28a CH=CH-OCH_3), 4.75 (bd, J = 7 Hz, 28b CH=CH-OCH_3), 3.57 (s, OCH_3), 1.95 (m, allylic), 0.98 (s, CH_3(2)).

MS: m/e calcd. for $C_{12}H_{20}O$: 180.1514, found: 180.1517(91), 65(100), 137(23), 133(48), 123(32), 121(25), 109(27), 107(38), 105(35), 95(20), 93(42), 91(43), 81(23), 79(36), 77(28), 75(86), 67(23), 55(32), 53(20).

ANALYSIS: calcd. for $C_{12}H_{20}O$: C 79.94, H 11.18; found: C 79.63, H 11.15.

4,4,10β-Trimethyl-7-methoxy-8,9-dicarbomethoxy-5,8-hexalin, 30a, b

A solution of dienes 28a, b (1.90 g, 10.6 mmole), and dimethyl acetylenedicarboxylate (2.56 g, 18.1 mmole) in anhydrous xylene (2 ml) were heated in a sealed tube at 130° for 7 days and then concentrated under reduced pressure to a brown liquid. Column chromatography (2% methanol in benzene) gave the viscous adducts 30a, b (1.53 g, 45%), R_f 0.6 ($CHCl_3$/PhH/CH_3OH, 10:10:1) as an equimixture of 30a (7α-methoxy) and 30b (7β-methoxy).

IR (film): 1730, 1670, 1640, 1435, 1260, 1210, 1080 cm^{-1}.

^{1}HMR($CDCl_3$): δ5.87 (d, J = 5.5 Hz, 30b H-6), 5.71 (d, J = 2.5 Hz, 30a H-6), 4.82 (d, J = 5.5 Hz, 30b H-7), 4.69 (d, J = 2.5 Hz, 30a H-7), 3.78 (s, $COOCH_3$), 3.32 (s, 30b, OCH_3), 3.26 (s, 30a, OCH_3), 1.64, 1.36, 1.27, 1.24, 1.22, 1.20 (s, CH_3).

MS: m/e calcd. for $C_{18}H_{26}O_5$: 322.1780, found: 322.1782(47), 290(100), 275(51), 263(61), 259(52), 258(29), 247(41), 245(21), 243(53), 231(47), 227(45), 207(22), 193(44), 177(26), 129(22), 115(24), 105(24), 91(24), 78(34), 75(49), 59(38), 55(35).

ANALYSIS: calcd. for $C_{18}H_{26}O_5$: C 67.06, H 8.13; found: C 66.66, H 7.91.

4,4-Dimethyl-8,9-dicarbomethoxy-5,7,9-tetralin, 31

Compound 31 was isolated from the column chromatography described for 30a, b, as a colorless liquid (0.35 g), R_f 0.8 ($CHCl_3$/PhH/CH_3OH, 10:10:1).

UV(CH_3OH) λ_{max}(ε): 242(10,400), 279(1,700), 287(1,700)nm.

IR (film): 1730, 1655, 1590, 1560, 1430, 1270 cm^{-1}.

^{1}HMR($CDCl_3$): δ7.82 (d, 1, J = 8 Hz, H-7(H-6)), 7.44 (d, 1, J = 8 Hz, H-6(H-7)), 3.91 (s, 3, $COOCH_3$), 3.83 (s, 3, $COOCH_3$), 1.28 (s, 6, CH_3).

MS: m/e calcd. for $C_{16}H_{24}O_4$: 280.1674, found: 280.1678(2), 276(6), 244(100), 229(38), 220(13).

4,4,10β-Trimethyl-8,9-dicarbomethoxy-trans-8-octalin, 36

Adducts 30a, b (0.42 g) and 10% Pd-C (0.12 g) was stirred in methanol (10 ml) at room temperature under a slight positive pressure of hydrogen. After 1 h, hydrogen uptake was very slow and the reaction mixture was filtered and the solvent distilled at atmospheric pressure. Preparative tlc ($CHCl_3/CH_3OH$, 30:1) gave octalin 36 as a colorless liquid (0.2 g, 52%), R_f 0.8.

IR(film): 1735, 1440, 1390, 1370, 1320, 1260, 1075, 1030 cm^{-1}.

^{1}HMR($CDCl_3$): δ3.68 (s, 3, $COOCH_3$), 3.64 (s, 3, $COOCH_3$), 2.35 (m, 2, $W_{\frac{1}{2}}$ = 13 Hz, H-7), 1.30 (s, 3, CH_3), 1.10 (s, 3, CH_3), 0.87 (s, 3, CH_3).

MS: m/e calcd. for $C_{17}H_{26}O_4$: 294.1831, found: 294.1828(44), 262(46), 234(54), 219(19), 175(14), 171(30), 139(26), 124(60), 123(23), 109(100), 105(24), 91(28), 81(20), 69(21), 59(20), 55(20).

4,4,10β-Trimethyl-8,9-dihydroxymethyl-trans-8-octalin, 39

Adducts 30a, b (350 mg, 1.1 mmole), platinum oxide (200-300 mg), and ether (5 ml) was stirred at room temperature under a slight positive pressure of hydrogen. After 4 h, the mixture was filtered and lithium aluminum hydride (110 mg, 2.4 mmole) was added slowly through a condenser into the ethereal solution of the hydrogenated

product. After stirring at room temperature for 20 min, water (10 ml) and 1N NaOH (10 ml) was added carefully. The resulting mixture was extracted with ether (2x) and the combined ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a colorless oil (250 mg). Column chromatography ($CHCl_3/CH_3OH$, 20:1) gave 39 as a colorless oil (57 mg, 22%), R_f 0.6 ($CHCl_3/CH_3OH$, 9:1).

IR($CHCl_3$): 3620, 3425, 1655, 1460, 1390, 1365, 990 cm^{-1}.

^{1}HMR($CDCl_3$): δ4.24 (s, 2, H-12(H-11), 4.08 (s, 2, H-11(H-12)), 1.10 (s, 3, CH_3), 1.01 (s, 3, CH_3), 0.92 (s, 3, CH_3).

^{13}CMR($CDCl_3$): 142.5, 137.6, 64.2, 58.6, 49.9, 41.9, 36.9, 34.5, 32.7, 31.9, 31.3, 28.6, 25.4, 20.2, 19.0 ppm.

MS: m/e calcd. for $C_{15}H_{26}O_2$: 238.1933, found: 238.1934(6), 220(41), 205(17), 203(20), 189(46), 177(25), 133(23), 123(42), 121(32), 119(37), 109(76), 107(57), 105(47), 95(82), 93(50), 91(51), 83(21), 81(75), 79(42), 77(28), 69(100), 67(44), 55(77), 53(22).

Chromatography also gave four other compounds: Isomers 40 as a colorless oil (18 mg, 7%), R_f 0.7, which was further purified and characterized as derivatives 42 and 43, and diols 41.

4,4,10β-Trimethyl-8,9-dihydroxymethyl-*trans*-decalin, 41

Compounds 41 were isolated from the chromatography of 39. Diols 41 were obtained as a white solid (93 mg, 35%), R_f 0.5 ($CHCl_3/CH_3OH$, 9:1).

IR($CHCl_3$): 3630, 3460, 1465, 1390, 1370, 1030 cm^{-1}.

^{1}HMR($CDCl_3$): δ3.75 (m, H-11, H-12), 1.19 (s, CH_3), 1.11 (s, CH_3), 0.85 (s, CH_3(2)), 0.81 (s, CH_3(2)).

MS: m/e calcd. for $C_{15}H_{28}O_2$: 240.2089, found: 240.2088(12), 222(12), 207(20), 192(21), 189(26), 135(25), 123(85), 121(31), 119(33), 109(76), 107(45), 105(33), 95(80), 93(47), 91(37), 81(79), 79(43), 77(25), 71(26), 69(100), 67(57), 57(22), 55(89), 53(25).

4,4,10β-Trimethyl-8,9-dihydroxymethyl-*trans*-7-octalin Acetonides, 42

Alcohols 40 (see experimental of 39) (62 mg) in 2,2-dimethoxypropane (1 ml) with a catalytic amount of *p*-TsOH·H_2O were stirred at room temperature for 5 h and then diluted with ether. The ethereal solution was washed with saturated $NaHCO_3$ solution (2x) and water; dried ($MgSO_4$); and concentrated under reduced pressure to give a colorless oil (66 mg). Preparative tlc of the crude products yielded 42 as a colorless oil (52 mg), R_f 0.9 ($CHCl_3/CH_3OH$, 20:1).

IR(film): 1460, 1380, 1375, 1220, 1160, 1080, 1015, 850, 840 cm^{-1}.

^{1}HMR($CDCl_3$): δ5.62 (m, H-7), 4.90, 4.26 (m, H-12), 3.7 (m, H-11).
^{13}CMR($CDCl_3$): 136.0, 134.7, 125.3, 124.7, 101.4, 67.4, 67.2, 62.4, 54.5, 50.9, 50.0, 48.2, 42.1, 39.6, 34.7, 34.1, 33.5, 31.5, 31.3, 28.1, 27.5, 25.9, 25.0, 24.5, 24.0, 23.6, 22.2, 19.3, 18.8, 14.7 ppm. (The six quaternary carbon signals were less intense and not observed.)
Chemical Ionization (NH_3) MS shows the M + 18 (m/e 296) and M + 35 (m/e 313) peaks.
MS: m/e calcd. for $C_{18}H_{30}O_2$: 278.2246,
found: 278.2244(3), 248(18), 190(100), 175(23), 119(25), 109(59), 105(33), 91(33), 55(20).

4,4,10β-Trimethyl-8,9-diacetoxymethyl-trans-7-octalin, 43

A solution of alcohols 40 (see experimental of 39) (25 mg) in pyridine (0.1 ml) with acetic anhydride (0.1 ml) was allowed to stand at room temperature overnight; diluted with pentane; washed with water (5x), and saturated $NaHCO_3$ solution; dried ($MgSO_4$); and concentrated under reduced pressure. Preparative tlc (pentane/ether, 4:1, double elution) gave the diacetates 43 as a colorless oil (8 mg), R_f 0.5 (pentane/ether, 2:1).
IR(film): 1740, 1460, 1380, 1365, 1240, 1025 cm^{-1}.
^{1}HMR($CDCl_3$): δ5.88 (m, H-7), 4.52 (bs, H-12), 4.2 (m, H-11), 2.03 (s, OAc), 2.00 (s, OAc), 1.21, 1.11, 0.90, 0.87, 0.85, 0.82 (s, CH_3).

^{13}CMR($CDCl_3$): 130.4, 128.8, 67.8(2), 64.0, 62.9, 49.3, 48.0, 46.9, 41.9, 39.3, 36.5, 35.8, 34.6, 33.1, 32.9, 31.4, 30.4, 29.0, 27.6, 25.4, 23.6, 21.8, 20.9(2), 19.8, 19.0, 18.6 ppm. (Due to the small amount of sample available, signals from C-4, C-8, C-10, and the carbonyl carbons were not observed.)

Chemical Ionization (NH_3) MS shows the 2M + 18 (m/e 662) and M + 18 (m/e 340) peaks.

MS: m/e calcd. for $C_{17}H_{26}O_2$: 262.1933,
found: 262.1937(31), 202(79), 189(33), 187(42), 159(30), 146(22), 133(40), 132(21), 124(23), 119(63), 118(34), 109(100), 107(21), 105(35), 95(21), 91(32), 81(23), 79(24), 69(27), 55(28).

4,4,10β-Trimethyl-8β,9β-dihydroxymethyl-8α,9α-epoxy-*trans*-decalin, 44

A solution of alkene 39 (9 mg, 0.038 mmole) and 85% *m*-chloroperbenzoic acid (11 mg, 0.054 mmole) in chloroform were refluxed for 40 min.; cooled; washed with 10% Na_2SO_3 solution, saturated $NaHCO_3$ solution (2x), and water; dried ($MgSO_4$); and concentrated under reduced pressure to give 44 as a colorless oil (9 mg, 94%), R_f 0.65 ($CHCl_3$/CH_3OH, 9:1).

IR($CHCl_3$): 3625, 3495, 1470, 1395, 1385, 1365, 1040 cm^{-1}.

^{1}HMR($CDCl_3$): δ3.63 (m, 4, H-11, H-12), 1.25 (s, 3, CH_3), 1.12 (s, 3, CH_3), 0.90 (s, 3, CH_3).

MS: m/e 254(3), 236(7), 177(21), 156(100), 139(37), 137(21), 123(26), 111(21), 109(22), 86(28), 84(44).

4,4,10β-Trimethyl-8,9-dihydroxymethyl-*trans*-8-octalin Acetonide, 46

A solution of diol 39 (45 mg) in 2,2-dimethoxypropane (0.5 ml) with a catalytic amount of *p*-TsOH·H_2O was allowed to stand at room temperature for 3 h. The resulting solution was then washed with saturated NaCl solution (2x), dried ($MgSO_4$), and concentrated under reduced pressure to give acetonide 46 as a colorless oil (47 mg, 90%).

IR(film): 1475, 1450, 1380, 1370, 1220, 1165, 1095, 1040, 835 cm^{-1}.

^{1}HMR($CDCl_3$): δ3.7-4.4 (m, 4, H-11, H-12), 1.88 (m, 2, H-7), 1.42 (s, 6, CH_3), 1.10 (s, 3, CH_3), 0.99 (s, 6, CH_3).

MS: m/e calcd. for $C_{18}H_{30}O_2$: 278.2246,

found: 278.2246(73), 220(73), 205(78), 192(41), 190(100), 187(31), 175(25), 149(29), 147(24), 135(28), 133(35), 123(43), 121(56), 119(58), 109(65), 107(78), 105(78), 95(69), 93(54), 91(64), 81(65), 79(49), 77(31), 72(37), 69(71), 67(43), 58(71), 55(65).

4,4,10β-Trimethyl-8β,9β-dihydroxymethyl-8α,9α-epoxy-*trans*-decalin Acetonide, 47

A solution of acetonide 46 (45 mg, 0.15 mmole) and 85% *m*-chloroperbenzoic acid (46 mg, 0.23 mmole) in methylene chloride (1 ml) was refluxed for 1.5 h; cooled; washed with 10% Na_2SO_3 solution, saturated $NaHCO_3$ solution, and water; dried ($MgSO_4$); and concentrated under reduced pressure to give quantitatively 47 as a colorless oil.

IR(film): 1465, 1450, 1380, 1375, 1220, 1165, 1105, 1080, 1035, 900, 885, 840.

^{1}HMR($CDCl_3$): δ3.5-4.1 (m, 4, H-11, H-12), 1.34, 1.27, 1.15, 1.08, 0.87 (s, 3 each, CH_3).

MS: m/e calcd. for $C_{18}H_{30}O_3$: 294.2195,
found: 294.2191(3), 279(29), 249(12), 206(40), 191(27), 123(65), 121(21), 119(27), 109(56), 107(39), 105(35), 95(48), 93(51), 91(61), 81(69), 79(66), 77(46), 69(82), 67(67), 65(23), 59(40), 55(100), 53(49).

Reaction of Epoxy Acetonide 47 with *n*-Bu-Li

To a stirred solution of 47 (~50 mg, 0.15 mmole) in anhydrous ether (2 ml) under nitrogen, was added *n*-BuLi/hexane (2.5 M, 0.15 ml, 0.37 mmole) at 0°. After stirring at 0° for 15 min, the reaction flask was allowed to warm slowly to room temperature and stirred further for 30 min. Water was added and the ethereal layer was washed with

water, dried ($MgSO_4$), and concentrated under reduced pressure to give a colorless oil (~50 mg).

IR($CHCl_3$): 3560, 3480, 1675, 1655, 1630, 1460, 1380, 1120, 830 cm^{-1}.

^{1}HMR($CDCl_3$): δ6.0 (s, vinyl of 49(50)), 5.8 (bdd, vinyl of 48).

Preparative tlc ($CHCl_3/CH_3OH$, 20:1) of the reaction products above gave only one major component as a colorless oil (11 mg, R_f 0.6), probably 49.

IR($CHCl_3$): 3580, 1630, 1455, 1380, 1375, 1120, 1100 cm^{-1}.

^{1}HMR($CDCl_3$): δ6.03 (s, 1, H-12), 3.75 (d, 1, J = 12 Hz, H-11), 3.44 (d, 1, J = 12 Hz, H-11), 1.44 (s, 9, CH_3), 1.06 (s, 3, CH_3), 0.94 (s, 3, CH_3).

Reaction of Epoxy Acetonide 47 with Lithium Diisopropylamide and Hydrolysis of the Reaction Products to give Furanoid 53

To a stirred solution of diisopropylamine (0.04 ml, 0.30 mmole) in anhydrous ether (1 ml) under nitrogen, was added *n*-BuLi/hexane (2.5 M, 0.10 ml, 0.25 mmole). After stirring for 5 min, a solution of 47 (15 mg, 0.05 mmole) in ether (1 ml) was added. The resulting solution was refluxed for 1 h and then quenched with saturated NaCl solution. The ethereal layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow

oil (12 mg), allylic alcohols, 49 and/or 50.

IR(film): 3480, 1660, 1460, 1450, 1370, 1220, 1120, 825 cm^{-1}.

^{1}HMR($CDCl_3$): δ5.86 (m, 1, vinyl), 4.14 (d, 1, J = 11.5 Hz, C(H)H-OR), 3.57 (d, 1, J = 11.5 Hz, C(H)H-OR), 1.37 (s, 6, CH_3), 1.22 (s, 3, CH_3), 1.16 (s, 3, CH_3), 0.86 (s, 3, CH_3).

The above allylic alcohol(s) were dissolved in THF/water (5:1, 1 ml) and a few drops of 1 N perchloric acid added. After standing at room temperature for 2 h, the THF was evaporated under reduced pressure and the residue diluted with ether. The ethereal layer was then washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated under reduced pressure to give an oil (8 mg), R_f 0.95 ($CHCl_3/CH_3OH$, 20:1), tentatively assigned structure 53.

IR($CHCl_3$): 1478, 1462, 1455, 1390, 1380, 1365, 1040, 890 cm^{-1}.

^{1}HMR($CDCl_3$): δ7.10 (s, 2, H-11, H-12), 1.15 (s, 3, CH_3), 0.93 (s, 3, CH_3), 0.62 (s, 3, CH_3).

MS: m/e calcd. for $C_{15}H_{22}O$: 218.1671, found: 218.1674(29), 203(100), 69(29).

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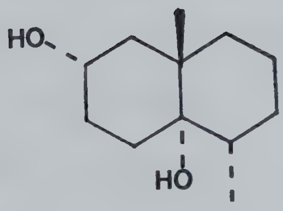
III. SYNTHESIS AND ^{13}CMR STUDY OF 10-METHYLDECALOLS[1]

INTRODUCTION

In an investigation of the culture broth of the bird's nest fungus Cyathus bulleri Brodie, the metabolite cybullol was isolated and 1 was proposed as its structure based on chemical and spectral evidence.[2] To obtain further support of the structure, particularly the stereochemistry of the ring junction, the ^{13}Cmr spectrum of cybullol (1) was determined. It was thought that the shielding of the angular methyl carbon could readily distinguish a 10-methyl-*trans*-decal-5-ol[*] from a 10-methyl-*cis*-decal-5-ol.[1b] It is known that when oxygen is bonded to a quaternary carbon, the antiperiplanar γ-carbons are only slightly deshielded (1-2 ppm) as



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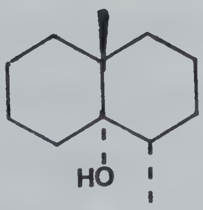

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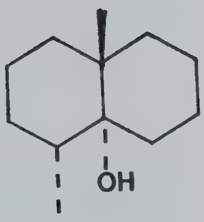
[*] Steroid numbering is used to name the compounds described in Part III of this thesis.

indicated in 1-substituted bicyclo[2.2.2]octanes and adamantanes,[3] and steroidal 5α,6-diols.[4] Furthermore, in 10-methyl-trans-decalins an equatorial hydroxyl substituent at C-2 deshields the angular methyl carbon by only 1 ppm.[5] Incorporating these small antiperiplanar γ effects, we therefore expected an angular methyl shielding near 18 ppm for the trans ring structure 1 since there was good evidence that the other substituents were equatorial. On the other hand, a cis ring junction for 1 with the γ gauche hydroxyl at C-5 would be expected to shield the angular methyl carbon by about 6 ppm relative to its position in 10-methyl-cis-decalin[6] to a value of about 22 ppm. Thus the ^{13}Cmr spectrum could be used to assign the stereochemistry of the ring junction.

A value of 21.1 ppm was obtained for the angular methyl shielding in cybullol which pointed to the structure with the cis ring junction. However, cybullol did in fact have the trans ring junction in structure 1 proven by its conversion[2] to the known metabolite (-)-geosmin (2), whose structure had been established by stereoselective synthesis.[7] This unusual[5,8] deshielding of the anti-periplanar angular methyl by the 5α-hydroxyl in cybullol initiated a study of the effect in related 10-methyl-decalols.

DISCUSSION AND RESULTS

To study the deshielding antiperiplanar effect of γ-substituents in ^{13}Cmr, we undertook the synthesis of (±)-geosmin (2) and some related 10-methyldecalols. In order to firmly establish the ring junction stereochemistry in these compounds, an unambiguous synthesis of at least one of the decalols 3 and 4[9] was necessary. The synthetic plan is outlined in Figure 1. In the fourth step of the scheme, the epoxide mixture 9 and 10 would be separated and characterized as their bromohydrin derivatives 11 and 12 respectively. The stereochemistry of each bromohydrin could be directly assigned from the nature of the C-4 hydrogen coupling in the ^{1}Hmr spectrum. The *trans* ring junction bromohydrin 11 would show only equatorial-axial and equatorial-equatorial coupling for the C-4 hydrogen, whereas the *cis* ring junction bormohydrin 12 would exhibit axial-axial and axial-equatorial coupling



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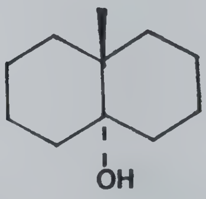

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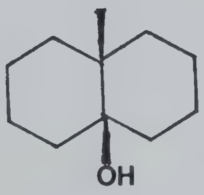

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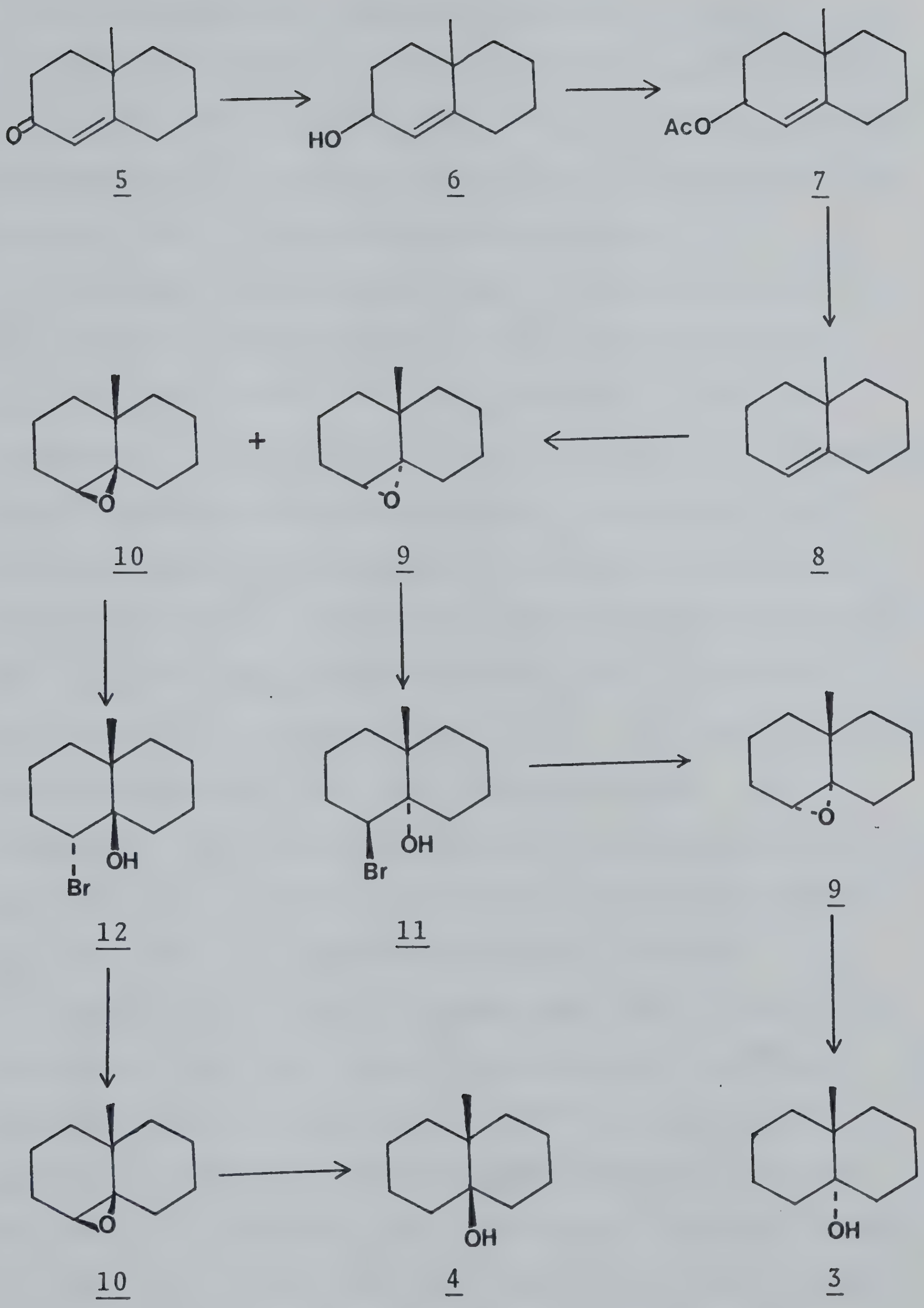
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Figure 1. The bromohydrin route to 10-methyldecal-5-ols.

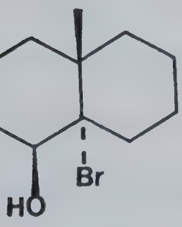
for the C-4 hydrogen. The bromohydrins 11 and 12 could be converted into their respective epoxides 9 and 10 in which the stereochemistry would be secure. Hydride reduction of the epoxides could then provide the desired decalols 3 and 4 of proven stereochemistry.

Octalone 5 was prepared under acidic conditions from 2-methylcyclohexanone and 4-chloro-2-butanone by the method of Heathcock.[10] The octalone 5 was then converted to octalin 8 via compounds 6 and 7 by succesive lithium aluminum hydride reduction, acetylation, and treatment with lithium/ethylamine according to Marshall and Hochstetler.[9] Epoxidation[9] of 8 with *m*-chloroperbenzoic acid gave the epoxide mixture 9 and 10 (70:30 respectively, as determined by ^{1}Hmr). The epoxide mixture was homogeneous by thin layer chromatography (tlc). Attempts to separate the mixture by gas chromatography (gc) employing various columns (OV-225, 5% Carbowax 20M, 20% Zonyl E7, 10% β,β'-oxydipropionitrile) failed.

Separation of the two components could however be effected at the next stage of the synthetic sequence. The bromohydrins 11 and 12 would likely be more readily separated. Treatment of the epoxide mixture 9 and 10 with HBr/HOAc was only partly successful, giving several products, one of which was the desired *cis* ring junction bromohydrin 12. Bromohydrin 11 was not detected.

It was anticipated the desired bromohydrins 11 and 12 could also be formed directly from octalin 8. Treatment of 8 with NBS and water in DMSO[11] gave numerous products which could not be identified after separation by preparative tlc. Different reagents such as N-bromoacetamide/sodium acetate in aqueous acetone[12] did not react with 8 to produce the desired bromohydrins 11 and 12.

It has been reported[13] that $\Delta^{9,11}$-steroids have been converted into 9-bromo-11-hydroxy steroids using N-bromoacetamide/perchloric acid in aqueous dioxane. Employing similar conditions the bromohydrins 13 and 14 could not be formed from 8. Numerous undesirable compounds were obtained from the reaction.



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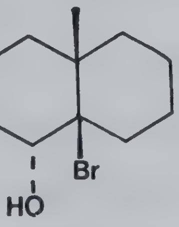

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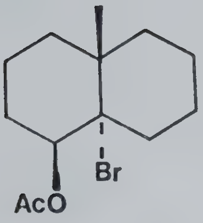
Treatment of octalin 8 with acetyl hypobromite in carbon tetrachloride[14] could yield the bromoacetates 15 and 16 which after separation, identification, and saponification



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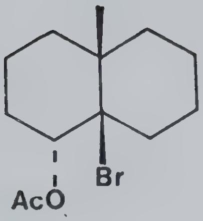

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would yield the stereochemically assigned epoxides 10 and 9 respectively. However the use of this method did not result in the desired bromoacetates, giving mostly unreacted 8.

Conversion of the epoxide mixture 9 and 10 into their corresponding diols 17 and 18 appeared to be an attractive alternative, as outlined in Figure 2. Diols 17 and 18 would be separated and characterized as planned for the bromohydrins above. The secondary hydroxyl groups in 17 and 18 could then be converted into leaving groups such as in mesylates 19 and 20 which upon base treatment would form the epoxides 9 and 10, direct precursors to the desired decalols 3 and 4, respectively.

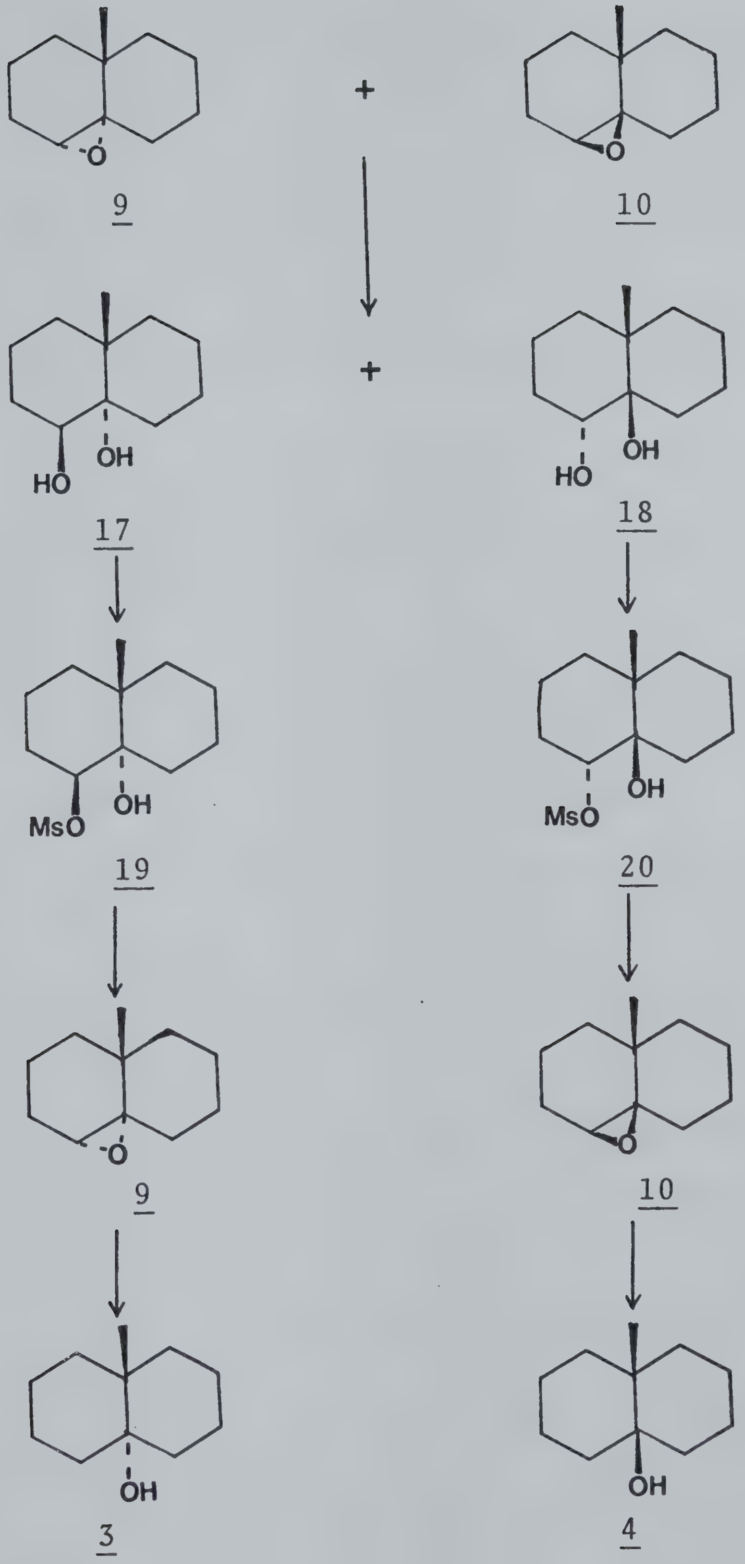

O
9
+
O
10
OH
HO
17
+
OH
HO
18
OH
MsO
19
OH
MsO
20
O
9
O
10
OH
3
OH
4

Figure 2. The diol route to 10-methyldecal-5-ols.

Reaction of the epoxide mixture 9 and 10 with aqueous perchloric acid in acetone[15] gave the crystalline diol 17 in 70% yield from 9. Diol 18 was isolated in only small amounts from the reaction. Characterization of the trans ring junction diol 17 is discussed first followed by a spectral analysis of the cis ring junction diol 18.

Diol 17 shows a sharp hydroxyl band (3630 cm^{-1}) in its high dilution ir spectrum as expected for a 1,2-trans-diaxial diol. In its ^{1}Hmr spectrum, the hydrogen geminal to the C-4 hydroxyl group appears as a triplet with a small coupling constant of 3 Hz, consistent with the anticipated equatorial-equatorial and equatorial-axial couplings with the C-3 hydrogens. The angular methyl group gives a singlet at δ1.23. It is known that chemical shifts in ^{1}Hmr depend on the nature of the solvent used. In the case of 10-methyl-trans-decal-5-ols, samples in pyridine solvent shift angular methyl signals downfield by 0.03 to 0.05 ppm relative to the samples in chloroform solvent.[16] The trans ring junction diol 17 however exhibits a downfield pyridine shift of 0.37 ppm. It was thought that the large shift is due to the dramatic effect of the 1,3-diaxial hydroxyl at C-4. A contact pyridine shift with the C-4 hydroxyl on the C-10 angular methyl can cause such a large

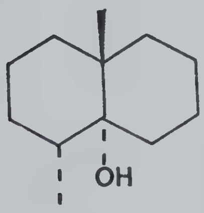
downfield shift.[16] Confirmation of this hypothesis was obtained by acetylation of the C-4 hydroxyl group. The monoacetyl derivative shows only a 0.09 ppm downfield pyridine shift. Although this pyridine shift is still larger than predicted for a 10-methyl-*trans*-decal-5-ol, this may be due simply to the anisotropy effect of the acetate carbonyl.

In the infrared, the *cis* ring junction diol *18* shows a slightly broadened hydroxyl absorption (3600 cm^{-1}) independent of concentration as indicated by a dilution study. This intramolecularly H-bonded absorption supports the 1,2-diequatorial nature of the hydroxyls in *18*. The hydrogen geminal to the C-4 hydroxyl group appears in the ^{1}Hmr spectrum as a multiplet with $W_{\frac{1}{2}}$ = 18 Hz, consistent with the axial-equatorial and axial-axial couplings expected from structure *18*. The angular methyl signal at δ0.96 has a downfield pyridine shift of 0.21 ppm, in accord with Wenkert's[16] prediction for the 10-methyl-*cis*-decal-5-ol system.

The next step in the above scheme (Figure 2) was to convert the secondary hydroxyls of *17* and *18* into good leaving groups. However, reactions were not carried out with diol *18* since it was available in only small quantities. *Trans* ring junction diol *17* was treated with mesyl chloride in pyridine. The mesylate *19*

was not isolated under the basic reaction conditions. Intermediate 19 underwent ring closure to produce epoxide 9 in moderate overall yield. Epoxide 9 was then converted quantitatively to the *trans* decalol 3 using lithium aluminum hydride. Thus we have achieved an unequivocal synthesis of the desired decalol 3 of proven stereochemistry. Decalol 3 can now be used as a reference for substituted 10-methyldecal-5-ols.[*]

We next set out to synthesize (±)-gesomin (2) and its epimers 21, 22,[9] and 23 for ^{13}Cmr analysis. A synthetic



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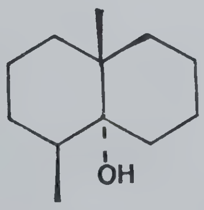

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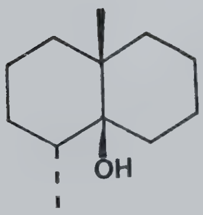

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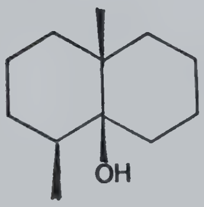

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[*] Decalols 3 and 4 were later synthesized by Dr. L.M. Browne via a stereochemically ambiguous, but more efficient , route.[1c] Octalone 5 was epoxidized and treated to Wharton reaction conditions. Subsequent separation of the allylic alcohols and hydrogenation gave 3 and 4.

approach to the dimethyldecalols 21 and 22 is outlined in Figure 3. Starting from octalone 24, epoxidation could yield the epoxy ketones 25a, b. Treatment of 25a, b to Wharton reaction conditions could then give the

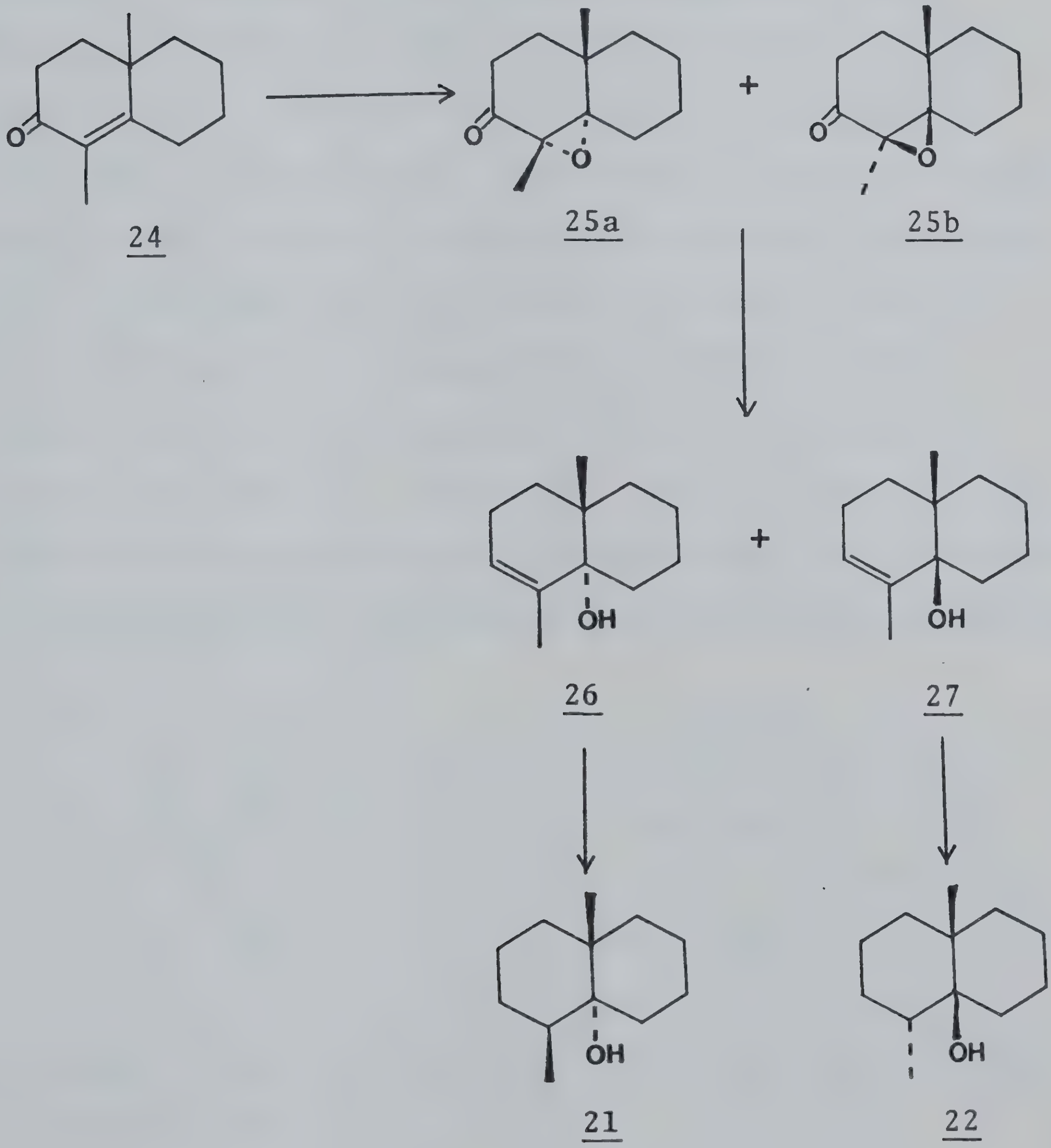
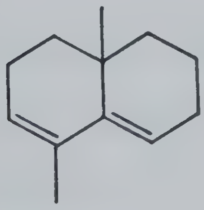


Figure 3. Synthetic plan to dimethyldecalols 21 and 22.

allylic alcohols 26 and 27. Separation of 26 and 27 followed by hydroxyl directed hydrogenation could then produce the desired dimethyldecalols 21 and 22.

Octalone 24 was prepared from 2-methylcyclohexanone and 1-chloro-3-pentanone according to the procedure of Zoretic.[17] Epoxidation of 24 was accomplished with alkaline hydrogen peroxide in a manner similar to that used by Kuehne and Nelson,[18] to obtain 25a and 25b in a 6:5 ratio, respectively. Treatment of the epoxy ketones 25a, b with hydrazine hydrate and acetic acid in methanol gave the Wharton reaction products 26 and 27. However 26 and 27 could not be separated by chromatography. Silica gel tlc and gc (Carbowax 20 M) provided 26, but none of the isomer 27. Diene 28, (see experimental) was also isolated from the above chromatography of the Wharton reaction products. Dehydration of alcohol 27 was probably the source of 28 since 27 could not be isolated from the Wharton reaction.



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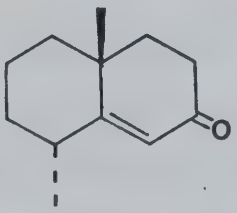

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Because the separation of 26 and 27 was not feasible, hydrogenation of the mixture to give 21 and 22 followed by separation of the products appeared to be an attractive alternative. Dehydration of 21 and 22 would be less likely since an allylic cation would no longer be possible as in allylic alcohols 26 and 27. Unfortunately hydrogenation of the mixture 26 and 27 was not totally successful. When 26 and 27 in ether was hydrogenated in the presence of platinum oxide at 50 psi, only 21 was obtained.* Compound 27 did not react under these conditions. Different conditions for the hydrogenation of 26 and 27 employing Pd-C/Et_3N/ether resulted in mostly hydrogenolyzed products and some starting material.

Compound 22 was later synthesized* from octalone 29[19] by successive epoxidation, Wharton, and hydrogenation reactions.

A synthetic plan (see Figure 4) to geosmin (2) and isomer 23 utilizes an alkylation reaction with lithium dimethylcuprate and α,β-epoxy oximes developed by Corey and co-workers.[20] Octalone 5 was epoxidized with alkaline hydrogen peroxide to give a mixture of the α- and

*The experiment was performed by Dr. L.M. Browne.

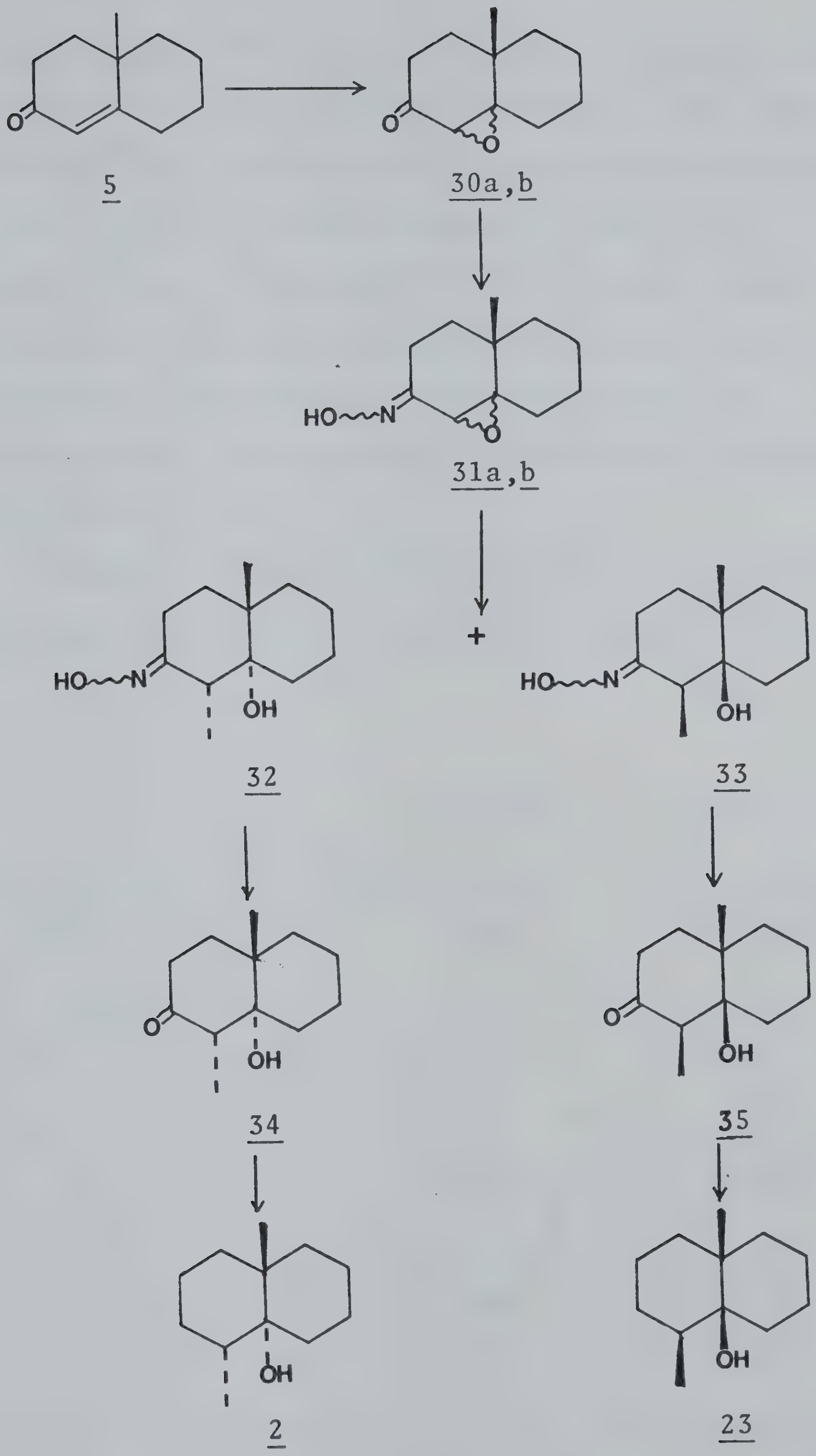

5
30a,b
31a,b
HO~N
O
OH
+
32
33
34
35
2
23

Figure 4. The alkylative oxime route to geosmin (2) and dimethyldecalol 23.

β-epoxides 30a and 30b respectively.[18] Epoxide 30b was formed in slightly higher yield than 30a. Oxime formation[20] by treatment of 30a, b with hydroxylamine hydrochloride and sodium acetate yielded 31a, b quantitatively. Treatment of the α,β-epoxy oximes 31a, b with lithium dimethylcuprate was expected to give the equatorially methylated products 32 and 33. Unfortunately, only starting materials were recovered from the reaction.

Another synthetic approach to geosmin (2) and isomer 23 is outlined in Figure 5. Dissolving metal

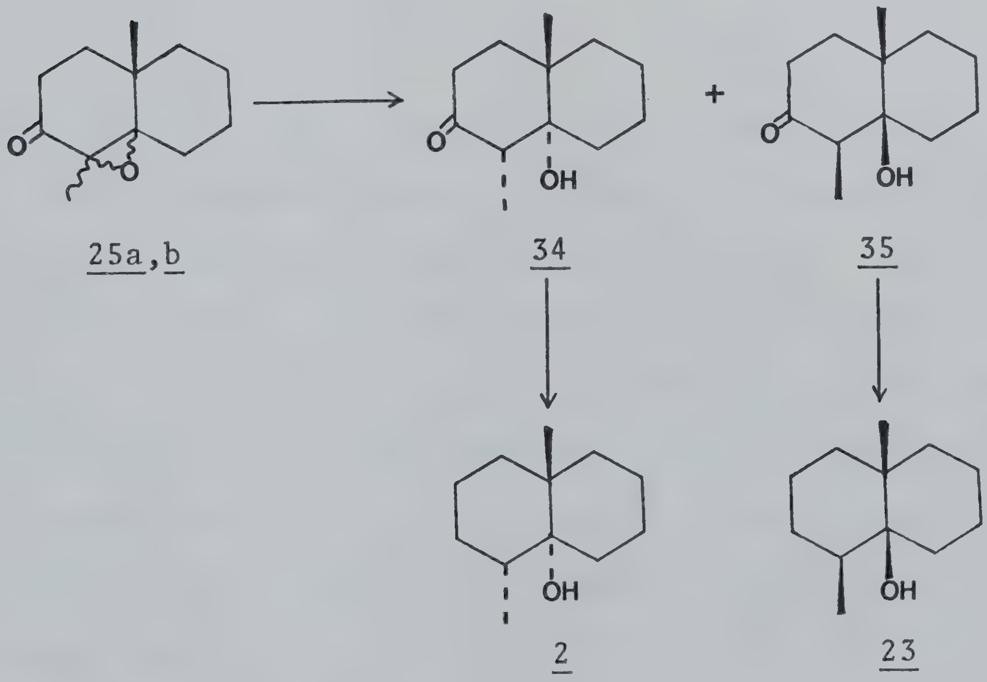
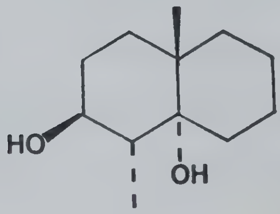


Figure 5. The dissolving metal route to geosmin (2) and dimethyldecalol 23.

reduction of epoxy ketones 25a, b could form the more stable equatorial methyl ketols 34 and 35. Transformation of the ketone function into methylene would then produce geosmin (2) and dimethyldecalol 23. The reduction of 25a, b to the β-ketols 34 and 35 was first tested using sodium in liquid ammonia. This reaction was unsuccessful, producing in low yield the over reduced diol 36 as the major product. Performing the reduction of the epoxy ketone mixture 25a, b with lithium in liquid ammonia gave much improved results. Ketol 34 was isolated in 53% yield (from 25a) after recrystallization. The mother liquors from the recrystallization contained about another 20% of 34 plus mostly unreacted 25a, b and some octalone 24. No β-ketol 35 was isolated. In an attempt to improve the yield of the dissolving metal reduction, lithium in the higher boiling solvent ethylamine was reacted with 25a, b. However this reaction resulted in mainly octalone 24 and diol 36.



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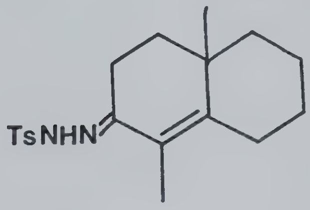
Reductive deoxygenation of the ketone function in 34 would provide (±)-geosmin (2). It was desirable to remove the carbonyl under mild and essentially neutral conditions in order to avoid dehydration of the sensitive β-hydroxyl group. The Caglioti[21] reaction appeared to be the method of choice. Repeated reduction attempts on 34 with tosyl hydrazine and sodium borohydride proved unsatisfactory. Only minor amounts of geosmin were produced. The major product was dehydrated tosylhydrazone 37 along with some starting material. An experiment designed to lead to the isolation of the intermediate hydroxy tosylhydrazone 38 after the first step of the Caglioti reaction yielded some 38, but about 40% of 38 had dehydrated to 37 even before all of the starting β-ketol 34 had reacted. Thus it appeared that the rate of dehydration of 38 was comparable to the rate of its formation. Part of the problem could be that the carbonyl function in 34 is somewhat sterically hindered being adjacent to a tertiary center. As described by Hutchins,[22] hindered carbonyls can be



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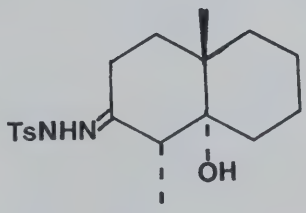

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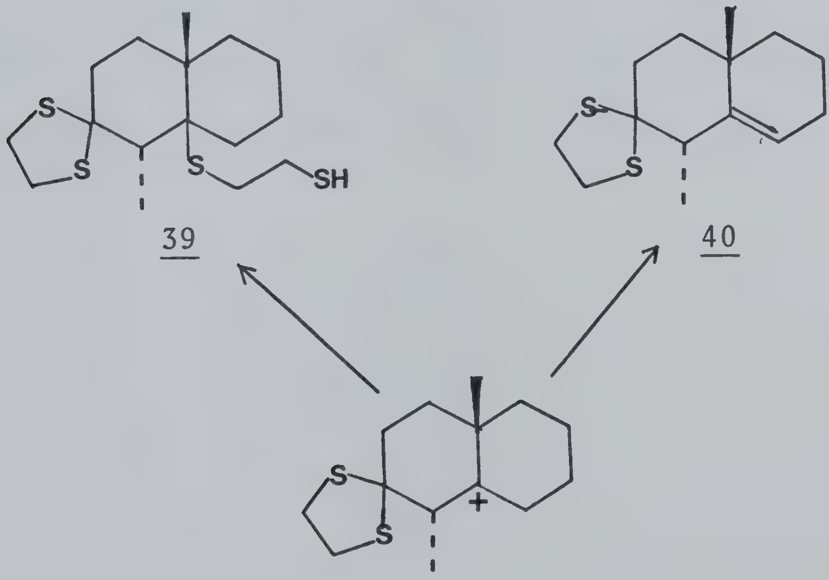
selectively deoxygenated with tosylhydrazine, p-toluenesulfonic acid, and sodium cyanoborohydride in dimethylformamide-sulfolane. This method was used with ketol 34, however the reaction gave only very small amounts of the desired geosmin (2).

Thioacetalization of 34 and subsequent desulfurization was a possible method for converting ketol 34 into geosmin. Employing mild conditions,[23] ie. ethanedithiol and boron trifluoride etherate in glacial acetic acid, ketol 34 gave compounds 39 and 40, presumably via intermediate 41.[24]



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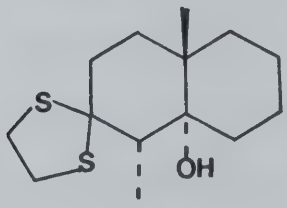
40

41

The formation of the undesirable products 39 and 40 was quite disheartening.

It appeared that deoxygenation of the β-ketol 34 would be very difficult if dehydration was such a rapid process. To monitor the dehydration rate of 34 under acidic conditions, ketol 34 was dissolved in glacial acetic acid and allowed to stand at room temperature for 5 minutes followed by immediate work-up. No dehydration products were detected. Only the starting β-ketol 34 was isolated. Buoyed by the results of this experiment, thioacetalization of 34 was attempted again; this time using only minute amounts of boron trifluoride etherate in glacial acetic acid with ethanedithiol, and with shorter reaction time. The hydroxy thioacetal 42 was produced in excellent yield! Treating 42 with



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Raney-nickel effected the required desulfurization to produce geosmin (2) quantitatively. The overall yield of (±)-geosmin from the readily available octalone 24 was 24%. The crystalline geosmin obtained was identical

in ir, ^{1}Hmr, ms, and tlc behavior with authentic (-)-geosmin.[2,25] Geosmin has not previously been obtained in crystalline form. It is interesting to note that the crystalline material has the characteristic 'earthy' aroma[26] of natural geosmin.

The typical odor of freshly plowed soil has intrigued scientists for almost a century. The compound geosmin (from the Greek "ge" = earth and "osme" = odor) has been found to be responsible for the odor associated with soil.[26a] In dilute aqueous solution geosmin has a characteristic 'earthy' aroma and an odor threshold of 5 parts in 10^{11}.[27] Geosmin was first isolated from the soil inhabiting microorganism actinomycetes by Gerber and Lechevalier.[26a] Since then geosmin has been identified as the substance causing the earthy taste and odor problems in water supplies,[25,28] trout,[29] beets,[30] and beans.[31] The structure and relative stereochemistry of geosmin was proven by Marshall and Hochstetler's synthesis of the racemic form.[7] However, the absolute stereochemistry of (-)-geosmin was not determined until 1976 when Ayer and Paice transformed the metabolite cybullol into (-)-geosmin.[2]

Compounds 2, 3, 4, 21, and 22 are now available for ^{13}Cmr analysis of the deshielding antiperiplanar effect of γ-substituents in decalin systems. The

shielding data for these compounds as well as decalins 43 to 60 are given in Figures 6 and 7 and Tables 1 and 2. The ^{13}Cmr signal assignments were determined with the aid of off-resonance and selective decoupling techniques, and simple additivity relationships.*

In the following discussion we will be concerned with the effect of substituents X on the γ-carbon in the fragment X-C_α-C_β-C_γ. More specifically, we will investigate the effect of the substituents OH and CH_3 on the antiperiplanar γ-carbons in decalin systems. Examination of the angular methyl ^{13}C shieldings in the compounds shown in Figure 6 will demonstrate the pronounced deshielding caused by an antiperiplanar hydroxyl group. In 3 the angular methyl carbon is deshielded by 4.7 ppm relative to 10-methyl-trans-decalin (43). The angular methyl carbon of 2 is deshielded by 4.6 ppm if we assume the 4α-methyl group has little effect on the shielding of the angular methyl group. Similarly, the angular methyl carbons of 45 and 1 exhibit a deshielding of 4.4 and 4.5 ppm respectively, by substitution of a 5α-hydroxyl group relative to 44. Decalone 47 also shows a rather large antiperiplanar γ effect of 5.9 ppm at the angular methyl carbon in relation to decalone 46.

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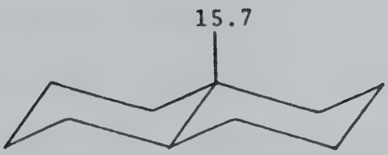
*The ^{13}Cmr spectra were measured and assigned by Professor J.B. Stothers and co-workers at the University of Western Ontario. The details of the signal assignments are discussed in reference 1c.



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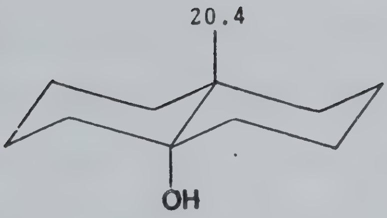

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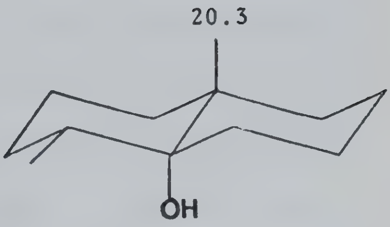

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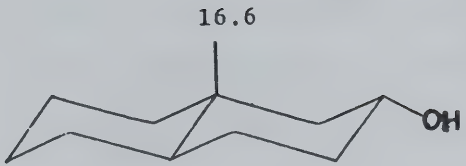

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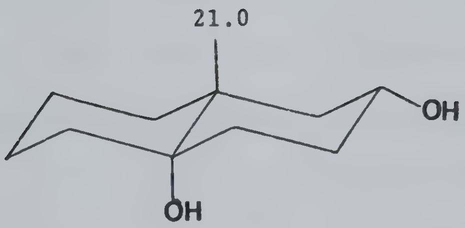

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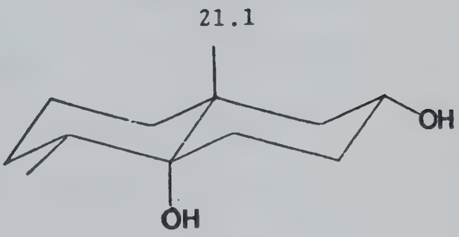

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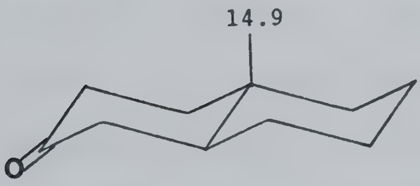

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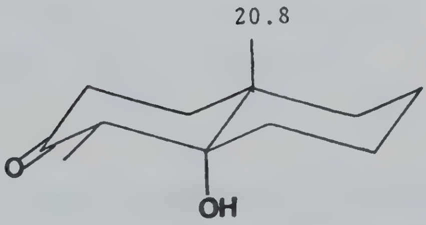

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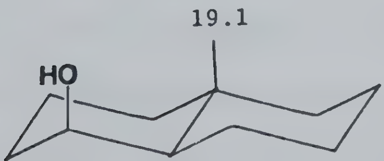

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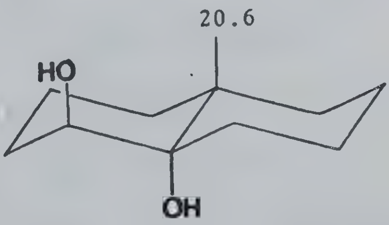

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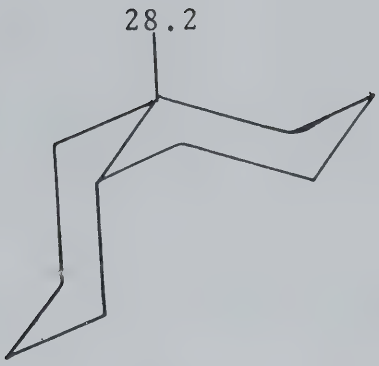
Figure 6. Angular methyl shieldings (ppm) of some 10-methyl-trans-decalins (taken from ref. 1b).

It is interesting to note that the deshielding effect is markedly attenuated if a second hydroxyl group is vicinal to the 5α-hydroxyl. Substitution of a 5α-hydroxyl on 48 leads to only a 1.5 ppm deshielding in the diol 49. The origin of the attenuation by a vicinal hydroxyl is not known but is substantiated in steroidal 5α,6-diols.[4] It is important to recognize that in the examples discussed above, the hydroxyl substituent is tertiary and the intervening α- and β-carbons in the fragment X-C-C-C are quaternary. It has been reported that in less highly substituted systems, antiperiplanar carbons to oxygen show an opposite shielding effect.[8]

Some 10-methyl-*cis*-decalins were also examined. Examples 4, 18, 22, 51, and 52 illustrated in Figure 7 show the expected upfield shift (~6 ppm) at the angular methyl carbon when γ *gauche* to a hydroxyl group, as compared to the parent system 50.

The degree of substitution of the intervening carbons in the fragment X-C-C-C greatly influences the nature of the antiperiplanar γ effect. This is illustrated by the shielding data for 43, 53, 54, and 55 listed in Table 1. The 1α-hydroxyl in 54 deshields the angular methyl carbon by 4.3 ppm relative to 53. This pronounced deshielding antiperiplanar γ effect is transmitted through fully substituted carbons. Decalol 55 however exhibits only a 0.4 ppm deshielding of the angular methyl carbon



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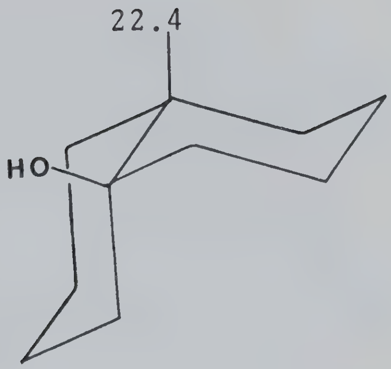

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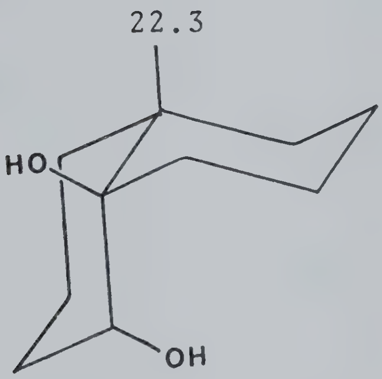

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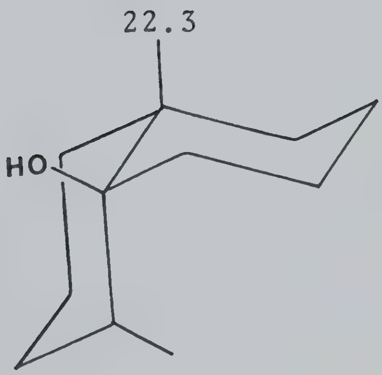

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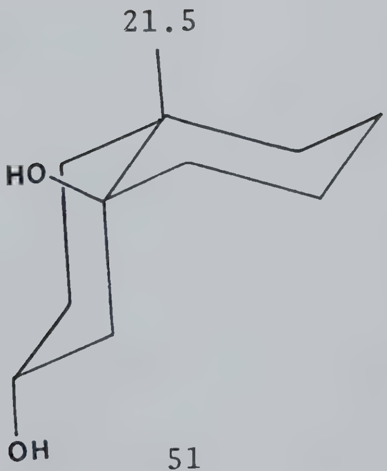

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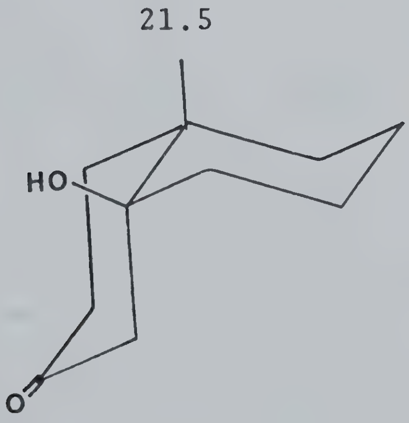

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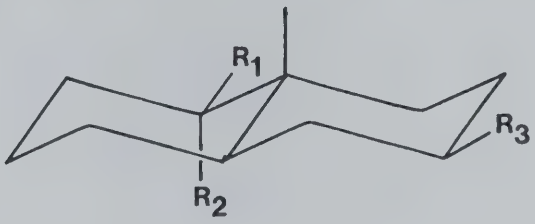
Figure 7. Angular methyl shieldings (ppm) of some 10-methyl-*cis*-decalins (taken from ref. 1b).

relative to 43. The drastic attenuation of the deshielding effect in 55 is due to the tertiary nature of the α-carbon.

So far we have only discussed the antiperiplanar effect of hydroxyl substituents on methyl carbons. The effect of hydroxyls on antiperiplanar methylene and methine carbons will now be examined. In less highly substituted decalin fragments where the hydroxyl is not bonded to a quaternary carbon the antiperiplanar effect is shielding. (This effect is in agreement with the results observed by Eliel and colleagues[8] for cyclohexane and norbornane systems.) For example, the 7β-decalol 56 (see Table 1) shows an upfield ^{13}C shielding on the antiperiplanar C-5 and C-9 of -2.7 and -2.1 ppm respectively with respect to decalin 43. Similarly 7β-decalol 57 shows C-5 methine and C-9 methylene shieldings of -2.5 and -1.9 ppm respectively in relation to decalin 53. In contrast, decalin systems in which the hydroxyl substituent is attached to a fully substituted carbon show an antiperiplanar deshielding effect. Assuming the 7β-hydroxyl of 58 has no influence on the C-3 methylene shielding, we can compare 58 with 1β-decalol 59. Thus the antiperiplanar C-3 of 59 is deshielded by 2.6 ppm by hydroxyl substitution at C-1. Note that in the less highly substituted 1β-decalol 60, C-3 is shielded by -2.8 ppm relative to 43.

Table 1

^{13}C shieldings[a] of some 10-methyl-*trans*-decalins



Compound	R_1	R_2	R_3
43	H	H	H
53	CH_3	H	H
54	CH_3	OH	H
55	H	OH	H
56	H	H	OH
57	CH_3	H	OH
58	H	CH_3	OH
59	OH	CH_3	H
60	OH	H	H

(continued...)

Table 1 (continued)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-10 CH_3	R_1	R_2
43	42.1	22.1	27.1	29.3	45.8	29.3	27.2	22.1	42.1	33.9	15.7		
53	43.6	31.3	(27.3)	(29.6)	47.0	(29.3)	(27.0)	22.4	39.1	36.8	10.5	15.2	
54	74.3	35.9	22.2	(29.2)	38.6	(28.9)	26.7	21.8	31.4	40.7	14.8	24.3	
55	75.4	(28.6)	20.5	(28.9)	37.6	(28.9)	26.8	21.9	34.9	38.3	16.1		
56[b]	41.1	21.9	26.7	28.8	43.1	38.1	71.0	31.2	40.0	33.0	15.7		
57	43.1	30.9	26.7	29.1	44.5	38.2	71.3	31.5	37.2	35.9	10.6	15.5	
58	35.6	29.3	20.9	29.3	38.5	38.5	71.1	31.4	35.0	35.3	18.5		14.1
59	75.2	37.6	23.5	(29.1)	41.2	(28.8)	26.7	21.9	32.0	41.5	12.2		22.8
60	79.6	30.4	24.4	28.1	44.2	28.1	26.8	21.7	37.3	39.2	9.8		

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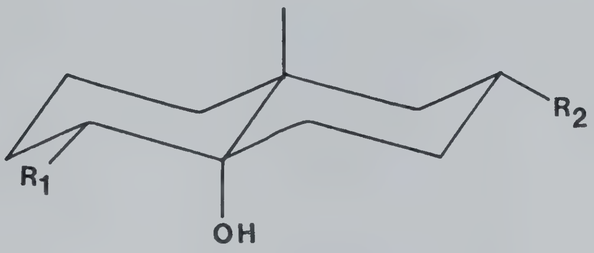
[a] Taken from reference 1c; in ppm from internal TMS in $CDCl_3$ solutions; similar values in parentheses may be interchanged.

[b] For ease of comparison, the carbon numbering is unconventional (see formula).

Table 2

^{13}C shieldings[a] of some 10-methyl-*trans*-decal-5-ols



Compound	R_1	R_2
1	CH_3	OH
2	CH_3	H
3	H	H
45	H	OH

(continued...)

Table 2 (continued)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-10 CH_3	R_1
1[b]	34.7	20.3	30.3	33.9	73.6	29.8	31.2	66.8	45.0	38.8	21.1	15.2
2	35.7	(20.7)	29.9	34.3	74.5	30.5	(20.8)	21.4	35.1	37.3	20.3	14.9
3	35.1	(21.1)	(20.8)	34.3	73.0	34.3	(20.8)	(21.1)	35.1	36.8	20.4	
45[b]	33.7	20.0	20.8	34.5	70.7	33.3	30.8	65.7	44.2	37.6	21.0	

---

[a] Taken from reference 1c; in ppm from internal TMS in $CDCl_3$ solutions; similar values in parentheses may be interchanged.

[b] For ease of comparison, the carbon numbering is unconventional (see formula).

Hydroxyl substituents also have a deshielding effect on antiperiplanar quaternary carbons in decalin systems (see Table 2). The 8α-hydroxyl substituent in 45 deshields the quaternary C-10 by 0.8 ppm relative to the parent compound 3. Furthermore, C-10 in decalol 1 is deshielded by 1.5 ppm in relation to 2. Though the observed deshieldings are small, it should be noted that the α-carbon is not fully substituted. Similar model compounds with quaternary α-carbons were not available for ^{13}Cmr analysis. It appears that for antiperiplanar quaternary carbons, the carbon attached to hydroxyl need not be fully substituted for a deshielding effect, unlike antiperiplanar methylene and methine carbons. Note that in compounds 45 and 1, the C-6 methylenes are in fact shielded by -1.0 and -0.7 ppm respectively, relative to their corresponding parent decalins 3 and 2.

In the antiperiplanar fragment X-C-C-C where X is methyl we observe deshielding effects less pronounced than in the case of hydroxyl substituted decalins (see Table 1). For example, the antiperiplanar angular methyl carbon in 58 is deshielded by 2.8 ppm by the 1α-methyl relative to 56. Similarly, the angular methyl carbon in 59 is deshielded by 2.4 ppm in comparison to decalin 60. Methyl substituents also deshield antiperiplanar methine carbons. In compounds 53, 54, and 57, C-5 is deshielded by 1.2, 1.0, and 1.4 ppm respectively, relative

to the corresponding parent compounds 43, 55, and 56. It is interesting that in the above methyl and methine shieldings the degree of substitution of the α-carbon attached to the methyl substituent does not influence the antiperiplanar γ effect as is the case for hydroxyl substituents.

However the C-3 methylene carbons of compounds 53, 57, and 54 are influenced by the degree of substitution of the α-carbon. In compounds 53 and 57 which have tertiary α-carbons the antiperiplanar C-3 is not shifted relative to compounds 43 and 56 respectively. But in compound 54 with a quaternary α-carbon the 1β-methyl deshields the C-3 methylene by 1.7 ppm relative to compound 55.

Methyl substitution also has a small deshielding influence on antiperiplanar quaternary carbons as indicated by compounds 1 and 2 (see Table 2). The 4α-methyl substituents in 1 and 2 deshield the antiperiplanar C-10 by 1.2 and 0.5 ppm respectively in comparison to the parent compounds 45 and 3.

The origin of the antiperiplanar effect in 5α-hydroxy steroids has been suggested[4] to arise from flattening of rings A and B to relieve steric interactions upon 5α-substitution thereby reducing the γ *gauche* effects of the methylene groups at the angular methyl group and decreasing its shielding. However in cholestan-3-ones,[1b]

a 5α-methyl substituent has a deshielding effect of 2.7 ppm whereas the small 5α-fluoro substituent has a larger effect of 4.4 ppm. Clearly steric interactions cannot be the only effects operating here. Electronic perturbations could be operative in the antiperiplanar γ effect. However it is difficult to explain the sign reversal of the shielding when comparing fully substituted and less highly substituted systems. Alternatively, Eliel and co-workers[8] favor a hyperconjugative mechanism to account for the shielding effect in less highly substituted systems. The electron pairs on the heteroatom substituent are proposed to interact hyperconjugatively with the C_α-C_β bond thereby increasing electron density at the antiperiplanar γ-carbon and causing an upfield shift. This explanation fails in fully substituted decalol fragments where a pronounced deshielding antiperiplanar γ effect is observed. A satisfactory explanation of the antiperiplanar γ effect has not yet been developed.

In summary, a number of tentative generalizations can be formulated based on the empirical evidence presented here for decalin systems.

(1) Hydroxyl groups deshield antiperiplanar methyl carbons in fully substituted systems by ~4-5 ppm. This effect is attenuated in less highly substituted systems.

(2) Hydroxyl groups deshield antiperiplanar methylene and methine carbons if the α-carbon is quaternary.

(3) Hydroxyl groups shield antiperiplanar methylene and methine carbons if the α-carbon is not quaternary.

(4) Hydroxyl groups deshield antiperiplanar quaternary carbons slightly if the α-carbon is tertiary.

(5) Methyl groups deshield antiperiplanar methyl, methylene, methine, and quaternary carbons if at least one of the intervening α- or β-carbons is quaternary. The deshielding effect is generally less pronounced than for hydroxyl substituents.

The overall trend of the antiperiplanar γ effect in going from fully substituted fragments X-C-C-C to less highly substituted systems is that of an attenuating deshielding effect to an opposite shielding effect. As a result of this γ-antiperiplanar effect, it is not always possible to distinguish *cis*-decalins from *trans*-decalins on the basis of the shift of the 10-methyl carbon.

EXPERIMENTAL

Mass spectra were recorded on an A.E.I. MS-9 or MS-12 mass spectrometer and are reported as m/e (relative intensity). Unless diagnostically significant only peaks at least 20% as intense as the base peak are reported. Infrared spectra were recorded on a Unicam SP1000 or a Perkin Elmer model 421 dual grating spectrophotometer. Proton magnetic resonance spectra were measured on Varian A-56/60 A or HA-100 spectrometers with TMS as internal standard. Carbon magnetic resonance spectra were measured on a Varian XL-100-15 system. All compounds were examined as 5-10% (w/v) solutions in deuteriochloroform using TMS as an internal reference. The precision of the ^{13}C shielding data is judged to be ±0.05 ppm. Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected.

Preparative tlc was carried out on 0.75 mm layers of silica gel G (W. Merck, Darmstadt) containing 1% electronic phosphor (General Electric, Cleveland), and materials were detected by spraying with 30% sulfuric acid and charring. Gas chromatography was carried out with an Aerograph model A-90-P3 chromatograph. Skellysolve B refers to Skelly Oil Company light petroleum, bp 62-70°C.

10β-Methyl-4β,5α-dihydroxydecalin, 17

To a stirred suspension of the epimeric epoxydecalins 9 and 10 (660 mg, 4.0 mmole), prepared according to Marshall and Hochstetler,[9] in acetone (35 ml) was added 7% aqueous perchloric acid (1.2 ml). After stirring at room temperature for 20 h, the mixture was concentrated under reduced pressure. The residue was poured into water and extracted with ether (2x). The combined ethereal extracts were washed with water, dried, and concentrated under reduced pressure to give a colorless oil (538 mg). Recrystallization from chloroform gave the white crystalline diol 17, mp 120-121° (344 mg, 67% yield based on the estimated 70:30 trans:cis ratio of isomers 9 and 10 in the starting epoxide mixture). Preparative tlc (pentane/ether, 1:2) of the mother liquors afforded an additional 31 mg of 17, R_f 0.3, giving a total yield of 73%.

IR(CCl_4): 3630, 1460, 1450, 1380, 1150, 1065, 960 cm^{-1}.

^{1}HMR($CDCl_3$): δ3.52 (t, 1, J = 13 Hz, H-4), 1.23 (s, 3, CH_3); (C_5D_5N): δ1.60 (s, 3, CH_3).

MS: m/e calcd. for $C_{11}H_{20}O_2$: 184.1463, found: 184.1469(20), 166(7), 148(7), 112(100), 111(29), 109(21), 97(48), 70(52), 67(29), 55(30), 43(26), 41(36).

ANALYSIS: calcd. for $C_{11}H_{20}O_2$: C 71.70, H 10.94; found: C 71.72, H 10.86.

10β-Methyl-4α,5β-dihydroxydecalin, 18

The preparative tlc of the mother liquors described in the experimental of 17 also gave a colorless oil (53 mg), R_f 0.2. The material was again subjected to preparative tlc (pentane/ether, 1:2, triple elution) to yield a colorless oil (35 mg) which subsequently crystallized. Recrystallization from Skellysolve B gave a white crystalline solid, mp 71-72° (15 mg).

IR(CCl_4): 3600, 1475, 1460, 1385, 1165, 1075, 1045, 990 cm^{-1}.

^{1}HMR($CDCl_3$): δ3.86 (m, $W_{1/2}$ = 16 Hz, H-4), 0.96 (s, 3, CH_3); (C_5D_5N): δ1.17 (s, 3, CH_3).

MS: m/e calcd. for $C_{11}H_{20}O_2$: 184.1463, found: 184.1462(19), 166(6), 151(5), 148(6), 112(100), 97(40), 70(43), 67(30), 55(44), 43(46), 41(53).

10β-Methyl-5α-hydroxy-4β-acetoxydecalin

A solution of 17 (40 mg) in pyridine (0.5 ml) and acetic anhydride (0.5 ml) was allowed to stand at room temperature for 1 day. The solution was then poured into water and extracted with ether (2x). The combined ethereal extracts were washed with water (2x), dried ($MgSO_4$), and concentrated under reduced pressure to give a white solid (45 mg) homogeneous by tlc (pentane/ether, 1:2), R_f 0.6. An analytical sample, mp 85-86° was

obtained by sublimation (60°/0.05 torr).

IR($CHCl_3$): 3620, 3520, 1730, 1460, 1370, 1270, 1060, 965 cm^{-1}.

^{1}HMR($CDCl_3$): δ4.66 (t, 1, J = 3 Hz, H-4), 2.06 (s, 3, OAc), 1.19 (s, 3, CH_3); (C_5H_5N): δ1.28 (s, 3, CH_3).

MS: m/e calcd. for $C_{13}H_{22}O_3$: 226.1569,
found: 226.1562(18), 184(13), 166(38), 112(100), 95(20), 81(27), 67(26), 55(34), 43(92), 41(44).

ANALYSIS: calcd. for $C_{13}O_{22}O_3$: C 68.99, H 9.80;
found: C 69.36, H 9.86.

10β-Methyl-4α,5α-epoxydecalin, 9

To diol 17 (34 mg, 0.18 mmole) in pyridine (3 ml) was added mesyl chloride (0.5 ml, 6.5 mmole) and the resulting solution was allowed to stand at -15° for 18 h. The resultant yellow reaction mixture was diluted with 5% aqueous KOH and extracted with pentane (2x). The combined pentane extracts were washed with water (5x), dried ($MgSO_4$), and the solvent was removed by distillation. Preparative tlc (pentane/ether, 2:1) gave the epoxide 9 (~20 mg, 67%), R_f 0.7.

IR($CDCl_3$): 1435, 1240, 1145, 1040, 830 cm^{-1}

^{1}HMR($CDCl_3$): δ2.90 (t, 1, J = 12 Hz, H-4), 1.11 (s, 3, CH_3).

MS: m/e calcd. for $C_{11}H_{18}O$: 166.1358,
found: 166.1362(6), 112(9), 86(63), 84(100), 47(26).

10β-Methyl-5α-hydroxydecalin, 3

The epoxydecalin 9 (15 mg, 0.09 mmole) in anhydrous ether (2 ml) was added dropwise to a stirred 0.5 M solution of $LiAlH_4$ (0.2 ml, 0.1 mmole) at 0° and stirred for 2 h under a nitrogen atmosphere. Water (0.5 ml), 1 N aqueous NaOH (0.5 ml), and water (1 ml) was added successively, followed by ether extraction (2x). The combined ethereal extracts were dried ($MgSO_4$), and the solvent was removed by distillation to give 3 (15 mg, 100%).

IR(film): 3480, 1450, 1370, 1170, 1005, 945, 880 cm^{-1}.

^{1}HMR($CDCl_3$): δ1.03 (s, 3, CH_3); (C_5D_5N): δ1.03 (s, 3, CH_3).

MS: m/e calcd. for $C_{11}H_{20}O$: 168.1514,

found: 168.1521(7), 112(88), 111(46), 109(25), 105(22), 97(28), 95(29), 93(20), 85(25), 83(43), 81(52), 74(28), 71(35), 69(100), 67(33), 59(52), 57(70), 55(68), 45(66), 43(59), 41(79).

4,10β-Dimethyl-4,5-epoxy-3-decalones, 25a, b[18]

To a rapidly stirred solution of octalone 24[17] (13.3 g) in methanol (300 ml) at 0° were added 30% H_2O_2 (24.0 ml) and 4 N aqueous NaOH (11.6 ml) dropwise and simultaneously. The solution was allowed to stand at -5° for 1 day and then was stirred at room temperature

for 3 days. The resulting mixture was then poured into water and extracted with ether (3x). The combined ethereal extracts were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to give epoxide mixture 25a, b (12.3 g, 85%) which was purified by distillation (90-93°/1 torr). Epoxides 25a and 25b were estimated by ^{1}Hmr to be in a ratio of 55:45 respectively.

IR(film): 1710, 1445, 1410, 1375, 1340, 1280, 1090, 1070, 1020, 905, 875, 850 cm^{-1}.

^{1}HMR($CDCl_3$): δ1.42 (s, 25b C-4 CH_3), 1.37 (s, 25a C-4 CH_3), 1.20 (s, 25b C-10 CH_3), 1.06 (s, 25a C-10 CH_3).

MS: m/e calcd. for $C_{12}H_{18}O_2$: 194.1307,
found: 194.1306(7), 176(18), 151(20), 109(100), 81(25), 67(37), 55(27), 43(57), 41(35).

ANALYSIS: calcd. for $C_{12}H_{18}O_2$: C 74.19, H 9.34;
found: C 73.87, H 9.15.

Wharton Reaction of Epoxydecalones 25a, b

To a solution of epoxydecalones 25a, b (480 mg) in methanol (15 mg) was added glacial acetic acid (0.5 ml) and hydrazine hydrate (1.0 ml). After standing at room temperature for 2.5 h, the yellow reaction mixture was poured into water and extracted with ether (2x). The combined ethereal extracts were then washed with 1 N HCl

and saturated $NaHCO_3$ solutions, dried ($MgSO_4$), and the solvents were removed by distillation. Preparative gc (10 ft. x $\frac{1}{4}$ in. stainless steel column packed with 5% Carbowax 20M on 80/100 Chromosorb W) of the crude products gave 4,10-dimethyl-3,5-hexalin (28, ~15% yield from crude the products).

UV(CH_3OH) λ_{max}: 242 nm.

IR(film): 2680, 1450, 1430, 1365, 1330, 1070, 990, 935, 875, 820 cm^{-1}.

^{1}HMR($CDCl_3$): δ5.54 (apparent bdd, 1, J = 7.5, 3.5 Hz, H-6), 5.50 (m, 1, $W_{\frac{1}{2}}$ = 9 Hz, H-3), 2.12 (m, 4, $W_{\frac{1}{2}}$ = 14 Hz, H-2, H-7), 1.76 (apparent q, 3, J = 1.5 Hz, C-4 CH_3), 0.98 (s, 3, C-10 CH_3).

MS: m/e calcd. for $C_{12}H_{18}$: 162.1409,
found: 162.1411(53), 147(100), 109(41), 105(65), 93(41), 91(56), 79(38), 77(31), 67(23), 43(30), 41(43), 39(30).

The above preparative gc of the crude products gave a very small amount of 26. Preparative tlc (pentane/ether, 2:1) of the crude products gave diene 28 and 4,10β-dimethyl-5α-hydroxy-3-octalin (26, ~45% yield from the crude products). The spectral data for 26 is given below.

IR($CHCl_3$): 3610, 1655, 1450, 1375, 1020, 940, 905 cm^{-1}.

^{1}HMR($CDCl_3$): δ5.43 (m, 1, $W_{\frac{1}{2}}$ = 8 Hz, H-3), 2.03 (m, 2, $W_{\frac{1}{2}}$ = 13 Hz, H-2), 1.73 (apparent q, 3, J = 2 Hz, C-4 CH_3), 1.00 (s, 3, C-10 CH_3).

MS: m/e calcd. for $C_{12}H_{20}O$: 180.1514,

found: 180.1517(63), 178(23), 165(27), 163(25), 123(100), 112(25), 109(31), 95(27), 91(22), 85(20), 82(35), 81(23), 67(21), 57(22), 55(38), 43(40), 41(40).

10β-Methyl-4,5-epoxy-3-decalone Oximes, 31a, b

To a stirred solution of epoxy ketones 30a, b[18] (1.80 g, 0.010 mole) in methanol (8 ml) at 0° was added sodium acetate (1.80 g, 0.022 mole) and hydroxylamine hydrochloride (0.76 g, 0.011 mole). After stirring at 0° for 40 min, the white reaction mixture was poured into water and extracted with ether (3x). The combined ethereal extracts were washed with water (2x), saturated $NaHCO_3$ solution (2x), and water (2x); dried ($MgSO_4$); and concentrated under reduced pressure to give 10β-methyl-4α,5α-epoxy-3-decalone oxime (31a) and 10β-methyl-4β-5β-epoxy-3-decalone oxime (31b) as an oil (1.96 g, 100%) in a ratio of 1:2 respectively.

IR($CHCl_3$): 3600, 3340, 1460(b), 1380, 1110, 955, 930, 865 cm^{-1}.

^{1}HMR($CDCl_3$): δ4.10, 3.36 (s, 31a H-4), 3.90, 3.31 (s, 31b, H-4), 1.14 (s, 31b CH_3), 1.07 (s, 31a, CH_3).

MS: m/e calcd. for $C_{11}H_{17}NO_2$: 195.1259, found: 195.1263(32), 178(27), 166(39), 166(39), 148(54), 133(23), 109(99), 107(45), 105(21), 95(21), 93(33), 91(32), 81(37), 79(43), 77(25), 67(100), 56(26), 55(75), 53(43), 43(35), 41(100), 39(71).

Treatment of Epoxy Oximes 31a, b with Lithium Dimethyl Cuprate

To a stirred suspension of purified CuI (1.6 g, 8.4 mmole) in anhydrous ether under nitrogen was added methyl lithium (22.7 ml, 2.2 M in ether, 50 mmoles) dropwise over 20 min at 0°. The resulting tan colored solution was stirred at -25° and a solution of 31a, b (1.0 g, 5.1 mmole) in anhydrous ether (40 ml) was added dropwise over 15 min. After stirring for 1 h at -25°, cold 10% acetic acid (60 ml) was added. The mixture was filtered and the organic layer was washed with saturated $NaHCO_3$ solution (2x) and water, dried ($MgSO_4$), and concentrated under reduced pressure to give an oil (0.77 g). Infrared, ^{1}Hmr, and tlc indicated the presence of predominantly starting material.

4α,10β-Dimethyl-5α-hydroxy-3-decalone, 34

Liquid ammonia (70 ml) was distilled through a NaOH drying tube into a dry flask containing the epoxydecalones 25a, b (1.14 g). Lithium (0.2 g) was added in pieces to

the stirred solution. After 6 h excess ammonium chloride was added and the ammonia allowed to evaporate. Water was added to the residue and the mixture was extracted with ether. The combined ethereal extracts were then washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to give a viscous oil (1.06 g) which subsequently crystallized. The solid was recrystallized from Skellysolve B to give 34 as white crystals, mp 109-110° (0.33 g, 53% from 25a).

IR($CHCl_3$): 3620, 3530, 1715, 1460, 1380, 1350, 1010, 960, 940, 885 cm^{-1}.

^{1}HMR($CDCl_3$): δ2.61 (q, 1, J = 7 Hz, H-4), δ2.4 (m, 1, H-2α), 2.05 (ddd, 1, J = 12.5, 12.5, 6 Hz, H-2β), 1.28 (s, 3, C-10 CH_3), 0.99 (d, 3, J = 6 Hz, C-4 CH_3); (C_5D_5N): δ1.26 (d, 3, J = 6 Hz, C-4 CH_3), 1.24 (s, 3, C-10 CH_3).

MS: m/e 196(19), 112(100), 97(22), 55(27), 41(20).

ANALYSIS: calcd. for $C_{12}H_{20}O_2$: C 73.43, H 10.27; found: C 73.72, H 10.44.

4α,10β-Dimethyl-5α-hydroxy-3-decalone Thioacetal, 42

The hydroxydecalone 34 (215 mg) was dissolved in glacial acetic acid (15 ml) and immediately 1,2-ethanedithiol (1.0 ml) and boron trifluoride etherate (0.10 ml) were added successively. After standing at room temperature for 15 min, the resulting solution was quickly worked-up

by dilution with brine and extraction with ether (2x). The combined ethereal extracts were then washed with 4 N NaOH and water, dried ($MgSO_4$), and concentrated under reduced pressure to yield the white crystalline 42 (287 mg, 97%), homogeneous by tlc. An analytical sample, mp 95-96° was obtained by recrystallization from Skellysolve B.

IR($CHCl_3$): 3610, 3500, 1455, 1385, 955, 890 cm^{-1}.

^{1}HMR($CDCl_3$): δ3.17 (m, 4, S-$C\underline{H}_2C\underline{H}_2$-S), 1.12 (d, 3, J = 6 Hz, C-4 CH_3), 1.07 (s, 3, C-10 CH_3).

MS: m/e calcd. for $C_{14}H_{24}OS_2$: 272.1268,
found: 272.1268(59), 254(56), 225(49), 132(58), 112(100), 55(45).

ANALYSIS: calcd. for $C_{14}H_{24}OS_2$: C 61.71, H 8.88;
found: C 61.71, H 8.78.

(±)-Geosmin, 2

Thioacetal 42 (92 mg), W-2 Raney-nickel (2 g), and absolute ethanol (10 ml) were stirred at room temperature for 1.5 h and then refluxed for 2 h. Additional Raney-nickel (1 g) was added and heating at reflux was continued further for 2 h. The mixture was then cooled, filtered, diluted with water, and extracted with pentane (3x). The combined organic layers were washed with saturated brine, dried ($MgSO_4$), and solvents removed by distillation to yield the colorless liquid geosmin (2) (62 mg, 100%), homogeneous by gc. On standing at 0° the liquid geosmin

crystallized, mp 78-82°. The spectroscopic data (ir, ^{1}Hmr, ms) obtained for synthetic geosmin is identical with an authentic sample.[2]

IR(CCl_4): 3640, 3530, 1460, 1450, 1380, 1180, 950, 885 cm^{-1}.

^{1}HMR($CDCl_3$): δ1.03 (s, 3, C-10 CH_3), 0.77 (d, 3, J = 6 Hz); (C_5D_5N): δ1.04 (s, 3, C-10 CH_3), 0.93 (d, 3, J = 6 Hz).

MS: m/e calcd. for $C_{12}H_{22}O$: 182.1670,

found: 182.1667(10), 164(1), 149(4), 112(100).

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